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Avaliação da frequência e dos fatores de risco para neoplasia colorretal na acromegalia

Bernardo Baêta Bastos Leão Maia

Dissertação de Mestrado apresentada ao Programada de Pós-graduação em Medicina, área de concentração em Endocrinologia, da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para obtenção do título de Mestre em Endocrinologia.

Orientadores:

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Resumo

Introdução: A acromegalia é uma doença sistêmica e crônica causada pela secreção excessiva e inapropriada dos hormônios GH (do inglês *growth hormone*, hormônio do crescimento) e IGF-I (do inglês *insulin-like growth factor type I*, fator de crescimento semelhante à insulina do tipo I), resultando em inúmeras complicações, como doenças cardiovasculares, respiratórias, metabólicas, osteoarticulares e, possivelmente, um risco aumentado de neoplasias. Ainda que os estudos sobre acromegalia e câncer permaneçam em debate, a maioria dos dados indica que a incidência de câncer colorretal (CCR) está aumentada nesta população, embora a magnitude deste risco não esteja clara. Desta forma, as diretrizes atuais preconizam o rastreio desta neoplasia no momento diagnóstico da acromegalia, independentemente da idade do paciente.

Objetivos: Avaliar a frequência de pólipos colônicos adenomatosos e CCR numa coorte de pacientes com acromegalia na primeira colonoscopia realizada e em exames subsequentes; correlacionar os fatores de risco pra CCR estabelecidos para a população geral, a atividade de doença na acromegalia e os achados colonoscópicos e analisar a relação da acromegalia como fator de risco para CCR e o melhor período para rastreamento desta neoplasia.

Métodos: Foram incluídos pacientes adultos (≥ 18 anos) com acromegalia devido a um adenoma hipofisário. Foi elaborado e aplicado um questionário envolvendo as características do acompanhamento da acromegalia e os fatores de risco relacionados ao CCR. Dados bioquímicos e colonoscópicos foram coletados por meio de prontuários médicos. Apenas colonoscopias totais e com preparo colônico satisfatório foram incluídas.

Resultados: Um total de 123 pacientes (62,6% mulheres e 37,4% homens) foram incluídos no estudo, com idade média de 43,1 anos ao diagnóstico da acromegalia e um tempo médio de seguimento de 13,7 anos. Em relação aos resultados da primeira colonoscopia, 80,5% apresentavam achados não neoplásicos, 14,6% adenomas não avançados, 3,3% adenomas avançados e 1,6% CCR. Ao final do estudo outro indivíduo foi diagnosticado com CCR, totalizando 3 (2,4%) pacientes. Nenhum paciente com menos de 50 anos apresentou lesão neoplásica à colonoscopia. Observamos uma relação estatisticamente significativa entre tabagismo ($p = 0,026$), idade ao diagnóstico da acromegalia ($p < 0,001$), idade na primeira colonoscopia ($p = 0,002$) e o risco de pólipos adenomatosos e/ou CCR na primeira colonoscopia.

Conclusão: Tabagismo e idade avançada foram os fatores positivamente relacionados a um maior risco de desenvolver lesões colônicas pré-malignas/ malignas na acromegalia dentre os fatores de risco relacionados ao CCR. A idade, particularmente após 50 anos, demonstrou ser a variável mais robusta, em congruência com o que é demonstrado na literatura com relação ao risco de

CCR na população geral. Nossos dados sugerem que a idade de rastreio para esta neoplasia na acromegalia deveria ser revisada.

Abstract

Introduction: Acromegaly is a chronic systemic disease caused by excessive inappropriate secretion of GH (growth hormone) and IGF-I (insulin-like growth factor type I) levels, resulting in many systemic complications, including cardiovascular, respiratory, metabolic, osteoarthropathy diseases, and a possible increased risk of neoplasias. While many studies on acromegaly and cancer remains a matter of debate, most data indicate that colorectal cancer (CRC) incidence is increased in this population, although the magnitude of this risk is still unclear. Therefore, current guidelines recommend screening for this neoplasm at the time of acromegaly diagnosis, regardless of the patient's age.

Objectives: To evaluate the frequency of colonic adenomatous polyps and CRC in a cohort of patients with acromegaly at the first colonoscopy performed and in the subsequent colonoscopies; to correlate the risk factors of CRC established for the general population and disease activity of acromegaly with the colonoscopy findings and to analyze the relationship of acromegaly as a risk factor for CRC and the best period for screening of this neoplasia.

Methods: Adult patients (≥ 18 years old) with acromegaly due to a pituitary adenoma were included. A questionnaire involving the characteristics of the follow-up of acromegaly and the risk factors related to CRC was created. Biochemical and colonoscopic data were collected through medical records. Only full-length colonoscopies with satisfactory colonic preparation were included.

Results: A total of 123 patients (62.6% female and 37.4% male) were included with a mean age at diagnosis of acromegaly of 43.1 years and a mean follow-up time of 13.7 years. Regarding the results of the baseline colonoscopy, 80.5% had non-neoplastic findings, 14.6% non-advanced adenomas, 3.3% advanced adenomas and 1.6% CRC. At the end of the study, another patient was diagnosed with CRC, totalizing 3 (2.4%). No patient under 50 years of age had a neoplastic lesion on colonoscopy. We observed a statistically significant relationship between smoking ($p = 0.026$), age at diagnosis of acromegaly ($p < 0.001$), age at baseline colonoscopy ($p = 0.002$), and risk of adenomatous polyps and/or CRC at initial colonoscopy.

Conclusions: Smoking and advanced age were the factors positively related to a higher risk of developing premalignant/ malignant colonic lesions in acromegaly, among the CRC related risk factors. Age, especially after 50 years, proved to be the most robust variable in this study, in line with what is shown in the literature regarding the CRC risk in the general population. Our data suggest that the screening age for this neoplasia in acromegaly should be reviewed.

Lista de abreviaturas

- GH: do inglês, *growth hormone*, hormônio do crescimento
- IGF-I: do inglês, *insulin-like growth factor type I*, fator de crescimento semelhante à insulina do tipo I
- CCR: câncer colorretal
- APC: do inglês, *adenomatous polyposis coli*
- KRAS: do inglês, *Kirsten rat sarcoma viral oncogene homolog*
- P53: do inglês, *tumor protein p53*
- IGF-II: do inglês, *insulin-like growth factor type II*, fator de crescimento semelhante à insulina do tipo II
- IGFBP: do inglês, IGF-*binding protein*, proteína ligadora de IGF
- SIR: do inglês, *standardized incidence ratio*
- NA: não avaliado
- BSG: do inglês, *British Society of Gastroenterology*
- AACE: do inglês, *American Association of Clinical Endocrinologists*
- ACG: do inglês, *Acromegaly Consensus Group*
- GRADE: do inglês, *Grading of Recommendations, Assessment, Development, and Evaluation*

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1- Introdução

A acromegalia é uma doença sistêmica e crônica causada pela secreção excessiva do hormônio do crescimento (GH) e, consequentemente, do fator de crescimento semelhante à insulina tipo I (IGF-I). Em aproximadamente 98% dos casos é causada por um somatotropinoma, ou seja, um adenoma hipofisário secretor de GH (1). É diagnosticada, em geral, entre a quarta e quinta décadas de vida, afetando indivíduos do sexo feminino e masculino em proporções similares. Devido ao seu caráter cronicamente progressivo e insidioso, há normalmente um atraso de 5 a 10 anos entre o início da sintomatologia e o diagnóstico, resultando em anos de morbidades sem o tratamento apropriado (2).

A acromegalia corresponde a um conjunto de complicações sistêmicas secundárias ao excesso de GH e IGF-I, incluindo doenças cardiovasculares, respiratórias, metabólicas e, possivelmente, um risco aumentado de doenças neoplásicas (3-6). Essas complicações são responsáveis pelo aumento da morbimortalidade, reduzindo a expectativa de vida do paciente em até 2 vezes, embora o controle efetivo dos níveis de GH e IGF-I seja capaz de trazer as taxas de mortalidade a níveis semelhantes aos da população geral (7). Embora nas últimas décadas as doenças cardiovasculares tenham representado a principal causa de morte da acromegalia, dados recentes demonstram que o câncer é atualmente a maior causa de mortalidade nestes indivíduos (8, 9).

O tratamento da acromegalia tem como objetivos o controle da hipersecreção de GH e IGF-I e do crescimento tumoral, a melhora dos sintomas e a preservação da função hipofisária (10). Atualmente dispomos de três modalidades terapêuticas: tratamento cirúrgico, farmacológico e radioterapia (10). A primeira linha de tratamento e única com capacidade curativa é a cirurgia transesfenoidal, contudo cerca de 50% dos pacientes que apresentam macroadenomas, principalmente aqueles com invasão do seio cavernoso, não alcançam cura, sendo necessário o tratamento medicamentoso no longo prazo (10, 11). Até o presente dispomos de três classes de medicamentos: ligantes do receptor de somatostatina, agonistas dopaminérgicos e antagonistas do receptor de GH (10, 12). Já a radioterapia é considerada terceira linha de tratamento, reservada como terapia adjuvante para casos de tumores agressivos não curados com a cirurgia e não controlados com o tratamento farmacológico (12).

1.1 Acromegalia e câncer

O papel do GH e IGF-I na carcinogênese e na progressão de tumores já existentes é um tema constantemente debatido entre especialistas, mas inúmeras incertezas ainda existem sobre o assunto (13-15).

Muitos estudos que abordam esta relação têm resultados contraditórios, que podem ser explicados por inúmeros fatores, como: análises de diferentes métodos epidemiológicos não comparáveis entre si (exemplo, caso-controle e estudos populacionais); ou vieses associados ao seu caráter retrospectivo, principalmente quando avaliamos trabalhos antigos, anteriores ao surgimento da farmacoterapia moderna, quando o paciente com acromegalia padecia de doenças cardiorrespiratórias, não alcançando faixas etárias normalmente relacionadas ao surgimento de neoplasias; ou pela ausência de uma população de controle apropriada e comparável, sem os ajustes apropriados dos fatores confundidores, como idade, sexo e fatores ambientais (16-20). Outro fator limitante corresponde ao fato de muitos estudos excluírem o registro de câncer antes do diagnóstico da acromegalia e, como este diagnóstico, em geral, ocorre muitos anos após o início da elevação dos níveis de GH e IGF-I, pode afetar negativamente a real estimativa do risco de neoplasias (16, 21). Além disso, como a acromegalia é uma doença rara, apenas estudos multicêntricos e/ou nacionais teriam melhor poder estatístico para demonstrar sua real relação de risco com neoplasias (17, 20).

Apesar das dificuldades técnicas e das controvérsias, os dados atuais indicam que não há um risco aumentado de câncer de pulmão, mama, próstata, dentre outros, quando comparado à população geral (3, 5, 16). Contudo, em relação ao câncer colorretal (CCR), os estudos e metanálises indicam um aumento leve a moderado de risco na acromegalia (6, 21-25).

1.2 Acromegalia e câncer colorretal

Na população geral, o CCR resulta do acúmulo de inúmeros processos, com uma via carcinogênica principal na qual o epitélio colônico normal se transforma em pólipos colônicos adenomatosos benignos, posteriormente em displásicos e, finalmente, em um câncer invasivo e/ou metastático (26, 27). Este processo de tumorigênese ocorre ao longo de 10 a 15 anos, envolvendo um acúmulo de mutações, ativação de oncogenes e inativação de genes supressores tumorais (26, 28, 29).

O primeiro passo nesta sequência de transformação de adenoma a CCR corresponde a inativação do gene *adenomatous polyposis coli* (APC), responsável pela regulação do crescimento celular através da inibição da proliferação e/ou da promoção de morte celular, gerando o desenvolvimento do adenoma (26, 28). Os processos que ocorrem subsequentemente são: mutação ativadora do *Kirsten rat sarcoma viral oncogene homolog* (KRAS), promovendo o crescimento do adenoma; perda da heterozigosidade no cromossomo 18q (lócus de supressão tumoral), através de instabilidade cromossomial, permitindo a progressão do adenoma; e inativação do gene supressor tumoral p53, que ativa a fase final de transição para carcinoma (26, 28, 30). Toda essa sequência

clássica está associada a outras mutações genéticas, instabilidade de microssatélites e alterações epigenéticas, que culminarão na formação patológica neoplásica (26, 28).

Quando estudamos o papel do GH na oncogênese é necessário entender que além de sua produção hipofisária e sua função endocrinológica, também há uma produção local extra hipofisária, responsável por ações autócrinas e parácrinas (31). No tecido colônico normal, a produção de GH é baixa, mas em condições predisponentes ao adenoma ou adenocarcinoma colônico se torna aumentada (31). Embora o GH não seja expresso por células epiteliais tumorais em adenocarcinoma colônico humano, é expresso no tecido fibroblástico que permeia a neoplasia colônica maligna (31). Já o receptor de GH é expresso tanto no epitélio colônico, quanto nas células estromais (31). Tanto os altos níveis de GH circulante (função endocrinológica), quanto seus níveis locais (função autócrina e parácrina) agem através dos receptores de GH, inibindo genes supressores tumorais (*p53*, *APC*), vias de reparo de DNA e a apoptose, além de estimular o risco de mutações, a proliferação celular, a angiogênese (o IGF-I é expresso nas células endoteliais durante a angiogênese, aumentando o fator de crescimento vascular endotelial, o principal responsável pela neovascularização tumoral) e a transição epitelial-mesenquimal, transformando um ambiente de mucosa intestinal normal em um microambiente pró-oncótico (31-33). Contudo, outros componentes do eixo somatotrófico, como o IGF-II e, principalmente, as proteínas de ligação ao IGF (IGFBP – IGF-*binding protein*), possuem um efeito antitumoral, através da inibição da mitogênese e estimulação da apoptose (34). Pacientes com acromegalia são expostos a altos níveis de GH, IGF-I e IGFBP por muitos anos antes do diagnóstico e, embora a ação final destas alterações seja complexa e ainda não totalmente entendida, os dados atuais apontam para um desbalanço a favor do desenvolvimento neoplásico.

Nas últimas décadas, ao analisarmos estudos de coorte de escala nacional, ou seja, estudos com maior acurácia para avaliar o risco de uma neoplasia em pacientes com doenças raras, observamos um aumento na razão de incidência padronizada de CCR na população com acromegalia em comparação com a população geral (21-25, 35). Dos seis trabalhos apresentados no **Quadro 1**, cinco demonstram um aumento leve a moderado, embora nem sempre com significância estatística. Isto talvez possa explicar porque estudos menores e, portanto, de menor poder estatístico, apresentem resultados heterogêneos. O único estudo que apresenta como resultado uma diminuição (não significativa) do risco de CCR quando comparada à população geral, pode ser explicado por algumas de suas limitações, como: utilização de uma pequena amostra proveniente do Registro Alemão de Acromegalia; parte dos dados de câncer foi obtida por entrevistas telefônicas, ou seja, nem sempre baseados em registros médicos de prontuários; 16% dos pacientes foram perdidos durante o seguimento do estudo (35).

Quadro 1 – Incidência de câncer colorretal na acromegalia em estudos de escalas nacionais.

Referência	País	Pacientes (N)	Seguimento (anos ou pessoas-anos)	Câncer Colorretal (N)	SIR câncer colorretal (95% IC)	*P* valor
(22)	Dinamarca, 2018	529	13.6	10 (1,9%)	1,4 (0,7-2,6)	NA
(23)	Itália, 2017	1512	10	20 (1,3%)	1,67 (1,07-2,58)	0,022
(35)	Alemanha, 2015	445	6656	4 (0,9%)	0,61 (0,17-1,55)	0,43
(24)	Finlândia, 2010	331	10,7	6 (1,8%)	1,9 (0,7-4,1)	NA
(25)	Suécia e Dinamarca, 2002	1634	Suécia = 10,3 Dinamarca = 9	23 (1,4%) [a] 13 (0,8%) [b]	2,6 (1,6-3,8) [a] 2,5 (1,3-4,2) [b]	NA
(21)	Reino Unido, 1998	1239	16778	12 (1%) [a] 4 (0,3%) [b]	1,68 (0,87-2,93) [a] 0,86 (0,23-2,20) [b]	0,06 [a] 0,69 [b]

SIR, standardized incidence ratio (razão de incidência padronizada); NA, não avaliado; [a], câncer de colon; [b], câncer de reto

Além disso, Dal e colaboradores (22) também realizaram uma metanálise envolvendo 23 estudos com o objetivo de analisar a razão de incidência padronizada (SIR) de câncer geral e seus subtipos na acromegalia. Avaliando apenas os estudos referentes à CCR (14 dos 23 estudos), foi observado um risco elevado para esta neoplasia (SIR = 2,6; 95% IC, 1,7 – 4,0), sem evidência de assimetria no gráfico de funil (teste de Egger com p = 0,67) (22). Vale notar que estratificando-se com base no desenho do estudo, o SIR demonstrou ser mais elevado nos estudos de centro único (SIR = 7,3; 95% IC, 2,6 – 20,6), comparando

com estudos multicêntricos (SIR = 2,0; 95% IC 1,3 – 3,1) e estudos de base populacional (SIR = 2,2; 95% IC, 1,7 – 3,0) (22). Esta diferença de riscos talvez possa ser explicada por alguns fatores: é possível que os pacientes de centro único representem casos difíceis com falha de tratamento anterior e mais comorbidades; é possível que os grupos de comparação dos estudos de centro único sejam derivados de programas de triagem, representando um risco de seleção de usuários saudáveis.

Portanto, apesar de nem sempre apresentar resultados homogêneos, a literatura atual aponta para um aumento de risco de CCR na acromegalia, refletindo nas recomendações de rastreio ativo desta neoplasia nas diretrizes e consensos.

1.3– Diretrizes de rastreio para câncer colorretal na acromegalia

Dentre as diretrizes atuais, as referentes a sociedades e grupos endocrinológicos, recomendam o início do rastreio para CCR no momento do diagnóstico da acromegalia, mas não têm consenso quanto a melhor periodicidade para a vigilância colonoscópica durante o acompanhamento destes pacientes. Os principais consensos na literatura sobre este tema são os publicados pela *British Society of Gastroenterology* (2010) (36); *American Association of Clinical Endocrinologists* (AACE) (2011) (37); *Pituitary Society* (2013) (4); *Endocrine Society* (2014) (7); e *Acromegaly Consensus Club* (2020) (ACG) (38). De acordo com a BSG, a colonoscopia de rastreio deve iniciar aos 40 anos de idade (36). Já a AACE, a *Pituitary Society*, a *Endocrine Society* e o ACG recomendam que o primeiro exame seja solicitado no momento do diagnóstico da acromegalia, independentemente da idade do indivíduo (4, 7, 37, 38). Enquanto isso, caso o paciente tenha uma colonoscopia inicial normal e níveis de IGF-I normais durante o seu acompanhamento, todas as sociedades recomendam um exame de vigilância a cada 10 anos, tal qual o preconizado para a população geral. Contudo, não há consenso entre as sociedades sobre o melhor intervalo para um novo exame, caso a colonoscopia inicial (ou qualquer uma subsequente) revele um adenoma e/ou os níveis de IGF-I estiverem acima do valor de referência para a idade (4, 7, 36-38) (**Quadro 2**).

Quadro 2 – Diretrizes atuais e suas recomendações para o rastreio e vigilância do câncer colorretal na acromegalia.

	BSG, 2010 (36)	**AACE, 2011 (37)**	***Pituitary Society*, 2013 (4)**	***Endocrine Society*, 2014 (7)**	**ACG, 2020 (38)**
Idade na colonoscopia inicial	**≥ 40 anos**	**No diagnóstico**	**No diagnóstico**	**No diagnóstico**	**No diagnóstico**
Colonoscopia inicial e níveis de IGF-I normais	**10-10 anos**	**10-10 anos**	**10-10 anos**	**10-10 anos**	**10-10 anos**
Adenoma na colonoscopia e/ou níveis de IGF-I elevados	**3-3 anos**	**5-5 anos**	**"Mais frequentemente"** [1]	**5-5 anos**	**"Mais frequentemente"** [1]

BSG: British Society of Gastroenterology; AACE: American Association of Clinical Endocrinologists; ACG: Acromegaly Consensus Group.

[1] A *Pituitary Society* e o ACG sugerem a realização da colonoscopia com maior frequência (sem especificar o intervalo de tempo), se os níveis de IGF-I permanecerem persistentemente elevados, ou se a colonoscopia anterior revelar anormalidade, ou se houver história familiar de CCR.

Ao avaliarmos as diferentes recomendações de cada sociedade, necessitamos observar o grau de evidência de cada uma com atenção, pois nenhuma estabelece um índice de forte qualidade de evidência. A BSG possui um grau de evidência B, caracterizado por evidência obtida de pelo menos um estudo controlado bem desenhado sem randomização, evidência obtida de pelo menos um outro estudo quase-experimental bem desenhado, ou evidência obtida de um estudo bem desenhado não experimental descritivo, como estudos comparativos, estudos de correlação e estudos de caso (36). A AACE apresenta um nível de evidência fraco (Grau C), baseado na opinião de especialistas e em dados de resultados experimentais e dados não experimentais (37). A *Pituitary Society*, a *Endocrine Society* e o ACG seguem a abordagem recomendada pelo grupo *Grading of Recommendations, Assessment, Development, and Evaluation* (GRADE) (39). A *Pituitary Society* apresenta um grau de recomendação forte para a idade no momento da colonoscopia de rastreio e para o intervalo de tempo entre os exames se os níveis de IGF-I persistirem elevados, mas apresenta uma recomendação discricionária caso a colonoscopia inicial e os níveis de IGF-I estejam normais (4). A *Endocrine Society* apresenta diretrizes referentes à

colonoscopia com um grau fraco de recomendação com estudos de baixa qualidade de evidência (7). O ACG tem uma recomendação fraca para a colonoscopia de rastreio no momento do diagnóstico da acromegalia (38).

Com relação a população geral, dados mais recentes apontam para uma tendência na diminuição da incidência de CCR nas pessoas ≥ 50 anos e um aumento no número de casos nos indivíduos mais jovens, embora o risco absoluto de desenvolver CCR seja menor em adultos < 50 anos (40). Desta forma, a maior parte das sociedades de gastroenterologia, oncologia e endoscopia preconizavam o início do rastreio de CCR na população geral a partir dos 50 anos de idade, com um grau de recomendação forte (Grau A) (41-44). Contudo, devido ao fato do aumento de casos de CCR em adultos mais jovens, dois grupos reduziram a idade recomendada para o início do rastreio: em 2018, a *American Cancer Society* emitiu uma recomendação "qualificada" para iniciar o rastreamento na população geral a partir dos 45 anos; e em 2021, a *United States Preventive Services Task Force* alterou sua recomendação para incluir a triagem de CCR em adultos a partir dos 45 anos (Grau B), embora mantenha a recomendação de rastreio a partir dos 50 anos com maior grau de evidência (Grau A) (42, 44). É importante notarmos que estas sociedades que têm por objetivo abordar o tema CCR e suas diretrizes de rastreio/ vigilância não citam a acromegalia como doença modificadora de conduta. Elas recomendam um rastreio mais precoce e vigilância mais intensa apenas para os pacientes pertencentes ao grupo de maior risco para CCR, uma vez que esta medida seria capaz de reduzir o risco de morte específica por esta neoplasia nesta população (27, 41, 43, 45, 46). No caso do CCR em sua forma esporádica, aqueles pertencentes a este grupo de maior risco seriam os que possuem história familiar em parentes de 1º grau com diagnóstico de CCR, sendo, portanto, recomendado o início do rastreio aos 40 anos de idade ou 10 anos antes do diagnóstico do parente (o que vier primeiro). Já para os grupos de alto risco na literatura (ex., portadores de polipose adenomatosa familiar, síndrome de Lynch ou doença inflamatória intestinal), recomenda-se uma prevenção muito mais rigorosa, iniciando o rastreio colonoscópico em idade mais precoce na vida (27, 45, 47). Na presença de outros fatores de risco que não são considerados de alto risco, não se recomenda mudança na idade de início de rastreio com colonoscopia.

1.4 – Fatores de risco para câncer colorretal

O complexo processo de transformação de lesões pré-malignas em malignas, responsável pela formação do CCR, ocorre gradualmente ao longo dos anos e é influenciado por inúmeros fatores genéticos e epigenéticos/ ambientais (26, 48). Diferente de outros tipos de neoplasia, como a de pulmão, os fatores de risco associados ao CCR muitas vezes ocorrem em associação nos estudos epidemiológicos, sendo difícil estabelecer um único fator com forte impacto para

ser responsável pela maioria dos casos de CCR (48). De qualquer forma, inúmeras evidências apontam para alguns fatores predisponentes e fatores protetores. Dentre os fatores de risco podemos citar: idade, sexo (masculino), história familiar de CCR, tabagismo, consumo excessivo de álcool, diabetes e obesidade (49-53). Já os fatores preventivos são: atividade física, uso de metformina e ácido acetil salicílico (AAS) (54-56).

A contribuição desses fatores de risco para o aumento do risco de CCR na acromegalia não está estabelecida.

2- Objetivos

- Avaliar a frequência de pólipos colônicos e de CCR numa coorte de paciente com acromegalia ao primeiro exame colonoscópico e/ou no seguimento;
- Correlacionar os fatores de risco para CCR, a atividade de doença na acromegalia e os achados colonoscópicos;
- Analisar a relação da acromegalia como fator de risco para CCR e o melhor período para rastreio desta neoplasia.

3- Artigo científico

3.1 – Artigo publicado

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REVIEW
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Acromegaly and Colorectal Neoplasm: An Update

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Acromegaly is a systemic disease caused by excessive inappropriate secretion of GH and IGF-I levels, resulting in many systemic complications, including cardiovascular, respiratory, metabolic diseases, and a possible increased risk of some neoplasias. Although many studies on acromegaly and cancer remain uncertain, most data indicate that colorectal cancer (CRC) incidence is increased in this population. The exact mechanism involved in the role of GH-IGF-I axis in CRC has not been fully explained, yet it is associated with local and circulating effects of GH and IGF-I on the colon, promoting angiogenesis, cell proliferation, risk of mutation, inhibition of tumor-suppressor genes and apoptosis, thus facilitating a tumor microenvironment. Nevertheless, population-based studies present controversial findings on CRC incidence and mortality. All worldwide guidelines and expert consensuses agree with the need for colonoscopic screening and surveillance in acromegaly, although there is no consensus regarding the best period to do this. This review aims to analyze the existing data on CRC and acromegaly, exploring its pathophysiology, epidemiological studies and their limitations, colonic polyp characteristics, overall cancer and CRC incidences and mortality, risk factors for colon cancer pathophysiology, and recommendation guideline aspects.

Keywords: acromegaly, colon cancer, colon polyp, mortality, colonoscopy

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INTRODUCTION

Acromegaly is a chronic systemic disease caused by the excessive secretion of growth hormone (GH) and consequently increased insulin-like growth factor type I (IGF-I) levels. In approximately 98% of cases, acromegaly is caused by a GH-secreting pituitary adenoma (somatotropinoma) (1, 2). Almost all epidemiologic studies are consistent in that acromegaly affects both sexes equally, although a Korean study showed that its incidence is slightly higher in females (1:1.3) (3–5). Nevertheless, all studies indicate that men are younger than women by 4.5 years at diagnosis, and it usually occurs at the fourth or fifth decades of life (6). Unfortunately, there is still a delay of 5-10 years between symptom initiation and diagnosis, resulting in years of morbidity and increased mortality when not properly treated (7).

Acromegaly is associated with many systemic complications secondary to untreated chronic excess GH and IGF-I, including cardiovascular and respiratory diseases, metabolic complications,

bone disease (especially vertebral fractures), arthropathy, and a possible increased risk of some neoplasias (8–10). These remarkable complications reduce the health-related quality of life and life expectancy of these patients, although the effective control of GH and IGF-I excess is able to reduce the burden of the disease and the mortality rates to normal levels observed in a general population (11–14). While cardiovascular disease has been the leading cause of mortality in the past decades, recent data suggest that cancer may be the main cause of death in acromegaly (15–17).

Although the discussion of the relationship between acromegaly and cancer dates to the last century, many uncertainties still remain in this field. Knowledge on this subject is not always homogeneous, but most studies indicate that colorectal cancer (CRC) is the main neoplasm associated with acromegaly (18, 19). Nevertheless, there is no consensus in the literature on the best approach for its screening and follow-up in these patients.

In this manuscript, we review CRC in acromegaly, discussing the GH-IGF-I axis in cancer (especially in CRC), risk factors for CRC, specific characteristics of colonic polyps, the limitations of colonoscopies in this population, data from epidemiological studies and their biases, and the different guideline recommendations for CRC screening in acromegaly.

MATERIALS AND METHODS

We searched the MEDLINE/PUBMED databases up to 1979 to 2022 to identify all relevant English language medical literature for studies under the search text terms; acromegaly AND (colorectal cancer OR colon cancer OR colon polyps OR colorectal polyps).

PATHOPHYSIOLOGY: SOMATOTROPHIC SYSTEM AND COLORECTAL CANCER

In nonacromegaly patients, most CRCs develop as a result of a multistep transformation of normal colonic epithelium to benign adenomatous colonic polyps, severe dysplasia and, finally, an invasive and/or metastatic cancer (20–22). The process involved in the tumorigenesis of sporadic forms of CRC, which takes approximately 10–15 years, requires an accumulation of genetic and epigenetic alterations in oncogenes and tumor suppressor genes (20, 22, 23).

The first step of this classical sequence is *adenomatous polyposis coli* (*APC*) gene inactivation, a "gatekeeper" gene that regulates growth by inhibiting proliferation or promoting cell death, which causes adenoma development (20, 23). This is followed by *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*) activating mutation, promoting adenoma growth; loss of heterozygosity at chromosome 18q (a tumor suppressor loci), due to chromosomal instability, a condition of malfunctioning segregation of sister chromatids during mitosis, allowing adenoma progression; and inactivation of the tumor-suppressor gene *p53*, which triggers the final transition to carcinoma (20, 23, 24). All these processes are associated with other genetic mutations, microsatellite instability, and epigenetic alterations, resulting in clinicopathological tumor features (20, 23).

When assessing the role of GH in oncogenesis, it is necessary to note that in addition to the endocrinological function related to pituitary production, it is also expressed in extrapituitary tissue, exercising autocrine and paracrine functions (25). In the normal colon, GH expression is low, but in conditions predisposing to colon adenoma or adenocarcinoma, it is exuberant (25). Although GH is not expressed within epithelial tumor cells in human colon adenocarcinoma, it is expressed in fibroblasts surrounding malignant colon carcinoma (25). In contrast, the GH receptor (GHR) is expressed in both colon epithelial and stromal cells (25). Currently, it has been postulated that both circulating (endocrine pattern) and local (autocrine/paracrine pattern) high GH levels, acting through the GHR, suppress *p53*, *APC*, DNA damage repair pathways and apoptosis and stimulate epithelial-mesenchymal transition by increasing the transcription of key metastasis-related genes, including proteins such as matrix metalloproteinases, cMYC (master regulator of cell cycle entry and proliferative metabolism), BCL-2 (B-cell lymphoma 2), and CHOP (C/EBP homologous protein 10), allowing a change in the normal intestinal mucosal environment in favor of a tumor microenvironment toward cell motility and invasion (25–27).

Another pathway that has been explored is that peroxisome proliferator-activated receptor gamma ($PPAR_\gamma$), a member of the nuclear hormone receptor superfamily that plays an important role in adipocyte differentiation and metabolism, also has an antiproliferative effect in several tissues, including colonic mucosa, where it is highly expressed (28). Although controversial, *in vitro* and animal studies suggests that $PPAR_\gamma$ has an antitumor effect in CRC as its activation is associated with inhibition of cell growth and its intestinal deficiency is associated with enhanced tumorigenicity in mice small intestine and colon (28). The molecular mechanism for the antineoplastic effect of $PPAR_\gamma$ activation remains incompletely enlightened. $PPAR_\gamma$ ligand treatment is associated with gene expressions changes involving: induction of apoptosis, by upregulating the proapoptotic protein BAX and downregulating the antiapoptotic BCL-2; cell proliferation inhibition through the decrease in cyclin D1 expression, a downstream effector of diverse proliferative and transforming signaling pathways, leading to the arrest of cell cycle progression; induction of cellular differentiation; and inhibition of angiogenesis in CRC, by decreasing vascular endothelial growth factor (VEGF) production and inhibiting capillary endothelial cell proliferation (28). Genetic studies showed that the presence of somatic loss-of-function mutations in the gene encoding $PPAR_\gamma$ contributes to colonic tumor development (29). Although some studies failed to detect any mutation of $PPAR_\gamma$ of colonic tissue in patients with acromegaly, others have observed that patients with active, untreated acromegaly had lower levels of $PPAR_\gamma$ expression in colonic mucosa than those with cured disease (30, 31). There is still a need for further studies,

but this might have the same role of the somatic mutations in PPARγ, playing a role in the development and/or progression of these cancers in nonacromegaly patients (29).

In addition to the GH-IGF-I axis being able to favor tumor development, it increases the risk of mutations, stimulates cell proliferation and angiogenesis (IGF-I is expressed in endothelial cells during angiogenesis and increases vascular endothelial growth factor, the main proangiogenic factor responsible for neovascularization), invasion, and metastasis; other components of the somatotropic system, such as IGF-II and IGF binding proteins (IGFBPs), exert an antitumoral effect by stimulating apoptosis and inhibiting mitogenesis, although the strength of these actions are weaker (27, 32–35).

The final action of this axis is complex and not yet fully understood, although the data indicate that there is an imbalance in favor of neoplastic development (**Figure 1**).

RISK FACTORS FOR COLON CANCER PATHOPHYSIOLOGY

The transformation of premalignant to malignant lesions, responsible for the development of CRC, corresponds to a complex process that occurs over years and is influenced by numerous factors (20, 36–38). Countless evidence points out that among these predisposing factors are diet, obesity, diabetes mellitus, dyslipidemia, physical inactivity, smoking, alcoholism, and genetic factors (36–38).

Among these factors, obesity, diabetes mellitus, and hypertriglyceridemia represent the ones with the most robust evidence, reflecting the main role of insulin resistance and hyperinsulinemia in association with its inflammatory markers in the carcinogenesis of the nonacromegaly population (37, 38). Although it is still debated, evidence points out that metformin has a protective role in patients with diabetes and insulin resistance as an anticancer chemoprevention agent (39, 40). The underlying mechanism of metformin antitumoral activity is not fully understood, but its action in reducing insulin levels and inhibiting phosphorylation of IGF-I receptor/insulin receptor and its pathways inhibition of cell proliferation and growth, as well as inducing apoptosis, have an important role (41, 42). Insulin promotes tumorigenesis by direct and indirect mechanisms, including one referring to the increase in circulating levels of IGF-I and IGF-II, through the reduction of IGFBPs (43). In addition, it is known that IGF-I, IGF-II, and insulin can cross-bind to each other's receptors with a lower affinity than with their original receptor due to the homology presented between them (34). The similarity between IGF-I receptor (IGF-IR) and insulin receptor (IR) allows the formation of hybrid receptors, which have a higher affinity for IGF-I than insulin (34). The biological significance of this is not entirely known, but it may be implicated in a greater activation of the IGF-IR pathway and its consequent mitogenic activity.

In CRC, evidence points out that activation of the IR pathway by insulin promotes cell growth and proliferation and that activation of the same signaling route (IR) by IGFs contributes to the oncogenic process by decreasing apoptosis and stimulating angiogenesis, cell proliferation and migration (44, 45). These comorbidities are very often present in acromegaly, being related to disease activity and/or its treatment, and might contribute to an increased risk of CRC.

OVERALL CANCER AND COLORECTAL CANCER AND POLYP INCIDENCE AND MORTALITY

In the past 20 years, data from laboratory, animal, and human model studies indicated that GH and IGF-I are associated with cancer, although findings from population-based studies present controversial results, explained by the numerous biases that will be mentioned ahead in this review (46, 47).

A review of six nationwide cohort studies that included a standardized incidence ratio (SIR) comparing the overall cancer rate and the CRC rate in patients with acromegaly with the general population indicated that five studies pointed to an increased risk of neoplasia, albeit moderate and not always

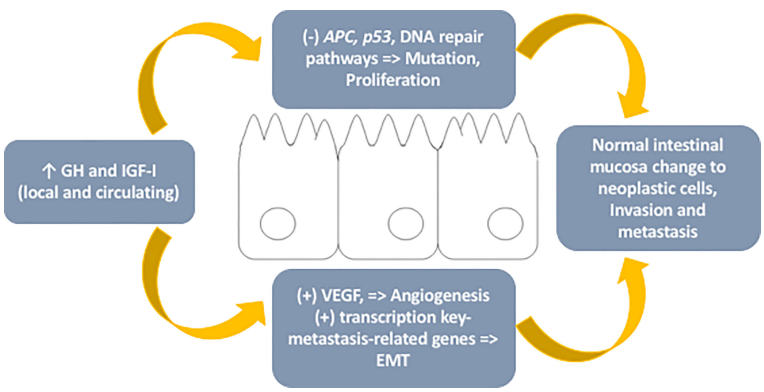

FIGURE 1 | – Schematic representation of mechanisms involved in the role of the GH-IGF-I axis in colorectal cancer. GH, growth hormone; IGF-I, insulin-like growth factor type I; APC, adenomatous polyposis coli gene; VEGF, vascular endothelial growth factor; EMT, epithelial-mesenchymal transition.

with statistical significance (**Table 1**) (18, 19, 48–51). This may explain why previous smaller studies (of less statistical power) present such incongruent results. Only one of these studies showed that CRC incidence was nonsignificantly lower than expected in the general population (48). This controversial result might be explained by some limitations of the work: only a small sample of the German Acromegaly Registry was used; part of cancer data was obtained by phone interviews and not always based on medical records; and 16% of patients were lost during follow-up.

Therefore, similar to overall cancer, the SIR of CRC compared to the general population has been variable, but most studies indicate an increased risk in acromegaly (18, 19, 49–51). This finding reflects the consensus of an active search for this comorbidity, although there is no uniform recommendation on how to perform this surveillance (8, 10, 13, 52–54).

Mortality in acromegaly has traditionally been related to its cardiovascular and respiratory complications (11, 51). However, current data point to a change in this paradigm, where neoplasia assumes the role of the main cause of mortality (15–17). This finding is accompanied by a general decrease in mortality when compared with older previous studies, reflecting the treatment progress made in recent years (16, 55). Thus, the decrease in overall mortality, the increase in life expectancy, and the aging of this population resulted in a consequent expected increase in the incidence of relevant age-dependent diseases, such as CRC.

Although the overall mortality rate, as well as cancer-related mortality, in controlled acromegaly are similar to that of the general population, those individuals with active disease and persistently high levels of GH and IGF-I will have higher all-cause mortality rates (between 1.5- and 2.0-fold), including those related to neoplasms, particularly CRC (15, 51, 56).

Although data related to CRC remain a subject of discussion, the increased risk for colon polyposis (either adenomatous or hyperplastic) in acromegaly is widely accepted (9). In addition, there is also a higher prevalence of diverticular disease, hemorrhoids, and the typical enlarged colon length (dolichocolon) (57).

Disease activity is directly related to the appearance of new polyps (9, 47). Excessive IGF-I levels, but not GH, and the duration of disease activity seem to correlate positively with the development of polyps in several studies (57, 58). However, there appears to be no relationship between IGF-I levels and polyp size (57).

These adenomatous polyps have some particular characteristics because, in general, they are larger, multiple, and more dysplastic than in the nonacromegaly population (59). They are also more common in men, in patients with an active disease duration greater than five years, in those with three or more skin tags, and in cases with a positive family history of colonic polyps (47, 60).

LIMITATIONS OF EPIDEMIOLOGICAL STUDIES AND OF COLONOSCOPY IN ACROMEGALY

The real relationship between acromegaly and cancer remains an unsolved question (46, 47, 61). Several data have reported that GH-IGF-I axis contributes to an important role in cancer development and progression, although the excess risk seems moderate (26, 33, 46, 47, 62).

Nevertheless, the studies that associate acromegaly and cancer have controversial results, often explained by the use of different epidemiological methods that are not comparable (case–control and population-based design); the retrospective nature of these studies, especially when considering that some studies date back to an era when treatment of acromegaly was less successful, so that patients with uncontrolled disease may have died by cardiovascular morbidity, for example, before entering the age when cancer is diagnosed; or the lack of an appropriate and comparable control population, which may not adjust results for

TABLE 1 | Overall cancer and colorectal cancer incidence in acromegaly in nationwide studies.

Country	Patients (N)	Follow-up (years or person-years)	Overall Cancer (N)	SIR overall cancer (95% CI)	*P* value(overall cancer incidence x general population)	Colorectal Cancer (N)	SIR colorectal cancer (95% CI)	*P* value (colon cancer incidence x general population)
Denmark, 2018 (18)	529	13.6	81 (15.3%)	1.1 (0.9-1.4)	NA	10 (12.3%)	1.4 (0.7-2.6)	NA
Italy, 2017 (19)	1512	10	124 (8.2%)	1.41 (1.18-1.68)	<0.001	20 (16.1%)	1.67 (1.1-2.6)	0.022
Germany, 2015 (48)	445	6656	46 (10.3%)	0.75 (0.55-1.0)	0.051	4 (8.7%)	0.61 (0.2-1.6) (p=0.43)	0.61
Finland, 2010 (49)	331	10.7	48 (14.5%)	1.5 (1.1-1.9)	NA	6 (12.5%)	1.9 (0.7-4.1)	NA
Sweden and Denmark, 2002 (50)	1634	Sweden = 10.3 Denmark = 9	177 (10.8%)	1.5 (1.3-1.8)	NA	23 (13.0%)[a] 13 (7.3%)[b]	2.6 (1.6-3.8)[a] 2.5 (1.3-4.2)[b]	NA
United Kingdom, 1998 (51)	1239	16778	79 (6.37%)	0.76 (0.60-0.95)	1	12 (15.2%)[a] 4 (5.1%)[b]	1.68 (0.9-2.9)[a] 0.86 (0.2-2.2)[b]	0.06[a] 0.69[b]

SIR, standardized incidence ratio; NA, not available; [a], colon cancer; [b], rectum cancer.

confounding factors, such as sex, age, and environmental factors (46, 47, 61, 63, 64). Another limiting factor is that many studies exclude the registration of cancer before the diagnosis of acromegaly, and as the diagnosis of this disease occurs many years after the real onset, it could have a negative impact on the actual estimate of neoplasm (47, 51). In addition, as acromegaly is a rare disease, only nationwide surveys may have the statistical power to demonstrate (or not) an excess risk of cancer (61, 64).

Another important confusing bias is related to the intensity of screening. This link between excess GH and IGF-I and the risk of cancer in some studies led to the recommendation of routine screening for neoplastic pathologies, including colorectal neoplasms, which influences the reported incidence rates (18, 26).

In addition to these study limitations, there are specific technical difficulties in assessing CRC in patients with acromegaly. In contrast to the general population, 25–40% of adenomatous polyps and 50% of adenocarcinomas in acromegaly are located in the ascending and transverse colon, so it is necessary to perform a total colonoscopy instead of a simple sigmoidoscopy (64–68). Another problem that can compromise the success of the exam is the difficulty in preparing the patient, since intestinal transit in acromegaly is slower than normal subjects. This can be explained by autonomic intestinal impairment due to vagal hypertonia, a hormonal imbalance influenced by the interactions between GH and ghrelin and the action of the increased IGF-I levels, which may stimulate the proliferation of intestinal epithelial cells (69). Gut motility disturbance can also occur in treated patients with somatostatin receptor ligands (69). Therefore, standard bowel preparations could lead to suboptimal results (70). Another major problem is that colon length and circumference are often increased (dolichocolon with megacolon), making complete intubation and identification of minor lesions more difficult (70, 71). Furthermore, there are some potentially harmful limitations inherent to this invasive procedure itself that may be enhanced in acromegaly patients, such as polypectomy bleeding (more common in the proximal colon), perforation (increased in the presence of diverticular disease – increased in acromegaly), and cardiopulmonary complications (cardiac arrythmias, hypotension, oxygen desaturation) (72).

All these considerations and technical complexity suggest the need for a trained and high-level skill endoscopist to perform this exam in patients with acromegaly.

GUIDELINES

There are numerous guidelines for the management of acromegaly patients, and practically all address the neoplasia risk. In relation to breast, prostate, lung, and other cancers, no increase in risk has been conclusively reported, and there is an agreement among all experts that surveillance should follow the same recommendations as for the general population (8, 9, 13, 47, 54). Specifically, with regard to the thyroid, current data do not support routine screening for thyroid cancer in acromegaly (13). Consistent with international guidelines, thyroid ultrasound is recommended in patients with clinically palpable nodules, and investigation with fine-needle aspiration cytology must respect the indications for the general population (8, 13, 54, 73).

However, in relation to CRC, there is no consensus regarding the best period for colonoscopic screening and surveillance during the follow-up of these patients. The most referenced guidelines on this topic in the literature are those published by the British Society of Gastroenterology (BSG) in 2010 (53); the American Association of Clinical Endocrinologists (AACE) in 2011 (54); the Pituitary Society in 2013 (10); the Endocrine Society in 2014 (13); and the Acromegaly Consensus Group (ACG) in 2019 (8).

According to the BSG, colonoscopy should begin at the age of 40 (52, 53). The AACE, Pituitary Society, Endocrine Society and ACG recommend that the first exam should be requested at the time of diagnosis, independent of the patient's age (8, 10, 13, 54). If a patient has normal initial colonoscopy and normal IGF-I levels, all societies recommend a new exam every 10 years. Nevertheless, there is no agreement on the best interval if the initial or any subsequent colonoscopy reveals an adenoma and/or if IGF-I is uncontrolled. The AACE and Endocrine Society recommend surveillance every 5 years; BSG suggests 3-year colonoscopy; the Pituitary Society advises performing the exam more frequently if IGF-I remains persistently elevated (without specifying the precising time) and proposes to follow in accordance with clinical guidelines for the general population if colonoscopy is abnormal (8, 10, 13, 52–54). It is worth noting that only the Pituitary Society cite a positive family history for colorectal cancer as a risk-modifying agent in acromegaly (8, 10). A summary of current guideline recommendations for surveillance colonoscopy in acromegaly patients is presented in **Table 2**.

Special attention should be given to the degree of recommendation when assessing different opinions provided by each society, since none establishes a strong or high-quality rate of evidence. For example, the BSG expresses a degree of recommendation B, characterized by evidence obtained from at least one well-designed controlled study without randomization, evidence obtained from at least one other type of well-designed quasi-experimental study, or evidence obtained from a well-designed nonexperimental descriptive study, such as comparative studies, correlation studies, and case studies (53). The AACE presents as a weak level of evidence (Grade C) based on expert opinion and on data from experimental results and nonexperimental data (54). The Pituitary Society followed the approach recommended by the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) group (74), and it has a strong degree of recommendation for the age of onset of colonoscopy and the exam time interval if the IGF-I level persists elevated (10), but it has a discretionary recommendation if the initial colonoscopy is normal and IGF-I level is normal (10). The Endocrine Society presents its colonoscopic guideline as a weak degree of recommendation with low-quality evidence studies (13). The ACG uses the same GRADE system and has a discretionary recommendation (8).

Due to the lack of conclusive data on the real incidence of malignancy and the relationship between CRC mortality and

TABLE 2 | Current guideline recommendations for surveillance colonoscopy in acromegaly.

	BSG, 2010 (53)	AACE, 2011 (54)	Pituitary, 2013 (10)	Endocrine Society, 2014 (13)	ACG, 2019 (8)
Age at initial colonoscopy	≥40 years	At the time of diagnosis	At the time of diagnosis	At the time of diagnosis	At the time of diagnosis
Normal initial colonoscopy and normal IGF-I	Every 10 years	Every 10 years	Every 10 years	Every 10 years	-
Adenoma in the colonoscopy and/or elevated IGF-I	Every 3 years	Every 5 years	"More frequently"	Every 5 years	-

BSG, British Society of Gastroenterology; AACE, American Association of Clinical Endocrinologists; ACG, Acromegaly Consensus Group.

acromegaly, there exists heterogeneity in the current surveillance recommendations for this neoplasm.

Current studies point to a higher incidence of CRC in increasingly younger nonacromegaly individuals, but screening for the general population still starts from the age of 50, as indicated by gastroenterology, oncology, and endoscopy societies (21, 36). The same guidelines recommend a more intense and earlier screening and follow-up only for patients allocated as the group at major risk for CRC, since this measure has been shown to reduce the risk of specific death for this neoplasm in this population (21, 75–79). For these individuals at increased risk, such as first-degree relatives of individuals diagnosed with CRC at young ages, the beginning of screening at younger ages is recommended (starting at age 40 years or 10 years before the youngest case in the family). For high-risk groups (familial adenomatous polyposis, hereditary nonpolyposis colon cancer, or inflammatory bowel disease), much more rigorous prevention programs are recommended, starting earlier in life (21, 75, 77, 78). It is important to note that none of these specific guidelines for CRC cite acromegaly as a screening modifying disease.

It is widely accepted that screening and follow-up colonoscopy are fundamental in acromegaly. However, the correct time for the first colonoscopy and for follow-up exams remains uncertain. There is little evidence to justify colonoscopy at the time of diagnosis in patients under the age 40, since in average-risk individuals (no prior diagnosis of CRC, adenomatous polyps, or inflammatory bowel disease; no personal diagnosis or family history of known genetic disorder that predisposes them to a high lifetime risk of CRC, such as Lynch syndrome or familial adenomatous polyposis), this exam starts at 50 years (21, 47, 80).

CONCLUSION

Although there are many biases and limitations in quantifying the overall CRC risk in the literature, current evidence suggests that acromegaly should be included in the group of factors associated with CRC, such as smoking, alcoholism, obesity, physical inactivity, diabetes mellitus, and others, which increase the risk for this neoplasm to a mild and moderate level (21, 36, 81).

Further studies on the topic are urgently needed for the adoption of a universal evidence-based guideline. In the near future, with more studies and data on this subject, the age of initial CRC screening in acromegaly and the interval between exams could possible be reviewed.

AUTHOR CONTRIBUTIONS

LK and BM reviewed the literature and wrote the manuscript. MG reviewed the manuscript and suggested the final changes. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

3.2 – Artigo a ser submetido para publicação

Title: Assessment of the frequency and risk factors for colorectal cancer in acromegaly

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Key Words: acromegaly; colorectal cancer; colorectal polyps; IGF-I

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Abstract

Introduction: Acromegaly is a chronic systemic disease caused by excessive inappropriate secretion of GH (growth hormone) and IGF-I (insulin-like growth factor type I) levels, resulting in many systemic complications, including cardiovascular, respiratory, metabolic, osteoarthropathy diseases, and a possible increased risk of neoplasias. While many studies on acromegaly and cancer remains a matter of debate, most data indicate that colorectal cancer (CRC) incidence is increased in this population, although the magnitude of this risk is still unclear.

Objectives: To evaluate the frequency of colonic adenomatous polyps and CRC in a cohort of patients with acromegaly at the first colonoscopy performed and in the subsequent colonoscopies; to correlate the risk factors of CRC established for the general population and disease activity of acromegaly with the colonoscopy findings and to analyze the relationship of acromegaly as a risk factor for CRC and the best period for screening of this neoplasia.

Methods: Adult patients (≥ 18 years old) with acromegaly due to a pituitary adenoma were included. A questionnaire involving the characteristics of the follow-up of acromegaly and the risk factors related to CRC was created. Biochemical and colonoscopic data were collected through medical records. Only full-length colonoscopies with satisfactory colonic preparation were included.

Results: A total of 123 patients (62.6% female and 37.4% male) were included with a mean age at diagnosis of acromegaly of 43.1 years and a mean follow-up time of 13.7 years. Regarding the results of the baseline colonoscopy, 80.5% had non-neoplastic findings, 14.6% non-advanced adenomas, 3.3% advanced adenomas and 1.6% CRC. At the end of the study, another patient was diagnosed with CRC, totalizing 3 (2.4%). No patient under 50 years of age had a neoplastic lesion on colonoscopy. We observed a positive statistically significant relationship between smoking ($p = 0.026$), age at diagnosis of acromegaly ($p < 0.001$), age at baseline colonoscopy ($p = 0.002$), and risk of adenomatous polyps and/or CRC at initial colonoscopy. Of the younger patients (< 45 years), only 3 had non-advanced adenomas and none had advanced adenomas and/or CRC.

Conclusions: Smoking and advanced age were the factors positively related to a higher risk of developing premalignant/ malignant colonic lesions in acromegaly, among the CRC related risk factors. Age, especially after 50 years, proved to be the most robust variable in this study, in line with what is shown in the literature regarding the CRC risk in the general population. Our data suggest that the screening age for this neoplasia in acromegaly should be reviewed.

Introduction

Acromegaly is a rare and chronic systemic disease caused by a hypersecretion of growth hormone (GH) and a consequently increased insulin-like growth factor type I (IGF-I) serum levels. The untreated chronic excess of GH and IGF-I in patients with acromegaly causes many systemic complications, including cardiovascular and respiratory diseases, metabolic complications, arthropathy, bone disease (especially vertebral fractures), and a possible increased risk of neoplasia (1-4). These complications are responsible for reducing the health-related quality of life and the life expectancy of these patients by up 2 times, although the effective hormonal control is able to decrease the burden of the disease and the mortality rates to similar levels observed in general population (5, 6). In the past decades, cardiovascular disease was the main cause of death in acromegaly, but recent data suggests that cancer may be the currently leading cause of mortality (7, 8).

Although the discussion of the relationship between GH, IGF-I and cancer dates to the last century, there are still numerous uncertainties in this subject (9, 10). The vast majority of the studies indicate that colorectal cancer (CRC) is the main neoplasm associated with acromegaly (2, 11, 12). Malignant transformation of normal colonic epithelium cells involves disruption of key cellular processes (13, 14). The GH-IGF-I system do not directly lead to malignant transformation, but GH-induced intracellular signaling may favor a tumor development environment by multiples ways, including: inhibition of tumor suppression genes (p53, *adenomatous polyposis coli* [APC]), DNA repair pathways and apoptosis; and increasing the risk of mutations, stimulating cell proliferation, angiogenesis and epithelial-mesenchymal transition (2, 15).

It is well established that the vast majority of CRC develop from a multistep transformation of normal colonic epithelium to benign adenomatous polyps, severe dysplasia, and finally, invasive and/or metastatic cancer. This is a complex process that occurs gradually over years (10-15 years) and is influenced by numerous genetic and epigenetic/ environmental factors (13, 16). Unlike others types of cancer, such as lung cancer, the risk factors for CRC often co-occur and interact in epidemiological studies, and because of that it is very difficult to establish a single risk factor with a strong impact as responsible for the majority of CRC cases (16). Apart from nonmodifiable risk factors, such as advanced age, (male) sex, and family history of CRC, the following modifiable risk factors have been identified: smoking, excessive alcohol consumption, diabetes mellitus and obesity (17-22). In addition, preventive factors in the literature include physical activity, use of metformin and acetylsalicylic acid (ASA) (23-25). Although there is still no consensus on the real risk of CRC in patients with acromegaly, most national and multicentric studies suggest that this risk is only slightly increased, but despite that, most acromegaly guidelines recommend CRC screening at the

time of diagnosis, regardless of the patient's age, as if acromegaly were a high-risk factor for this neoplasm (2, 5, 26, 27).

The aim of this study is to evaluate the frequency of colonic polyps and CRC in a cohort of patients with acromegaly at the first colonoscopy performed and in the subsequent colonoscopies, and to correlate the risk factors of CRC recognized in the literature and disease activity of acromegaly with the colonoscopy findings, since the influence of these risk factors in this specific population is not well established. Furthermore, to analyze the relationship of acromegaly as a risk factor for CRC and the best period for screening of this neoplasia.

Patients and methods

Study population

This study included adult patients (≥ 18 years old) diagnosed with acromegaly due to a pituitary adenoma recruited from the outpatient neuroendocrinology clinic of the Hospital Universitário Clementino Fraga Filho (HUCFF) – Universidade Federal do Rio de Janeiro (UFRJ) from April 2021 until August 2022. Acromegaly diagnosis was made based on clinical suspicion and biochemical confirmation according to guideline recommendations (5).

Study design

This was a retrospective cohort, single-center study. A questionnaire involving collection of clinical data was applied by a single trained examiner. This questionnaire involved simple and direct questions to the patients regarding the characteristics of the follow-up of acromegaly and the risk factors related to CRC. The rest of the information (biochemical and colonoscopic data) was collected through medical records.

Inclusion criteria

- Patients ≥ 18 years old.
- Biochemical and/or histopathological confirmation of acromegaly, according to recommended in guidelines (5).
- Full-length colonoscopy with satisfactory colonic preparation defined according to Boston scale ≥ 6 with cecal intubation confirmed by identification of the appendix orifice and the ileocecal valve (28).

Exclusion criteria

- Personal known history of inflammatory bowel disease and/or familial adenomatous polyposis.

Clinical, biochemical and colonoscopy variables

The following clinical, biochemical and colonoscopy variables were obtained through medical records and by a questionnaire applied by a trained examiner. The collection of such data aims to analyze the laboratory characteristics of GH and IGF-I levels, the risk factors related to CRC and the results of colonoscopy of the studied population.

The CRC risk factors investigated were:

- Smoking: assessment as smoking status - non-smokers (person who has never smoked or who smoked less than 100 cigarettes in lifetime), former smokers (person who smoked more than 100 cigarettes in lifetime, but has not smoked for at least the last 12 months), and current smokers (person who smoked more than 100 cigarettes in lifetime and is currently smoking or stopped for less than 12 months); and cumulative pack-years smoked, calculated as cumulative average of pack [packs per day multiplied by number of years during which smoking occurred (< 20, ≥ 20 pack-years)] (17, 18, 29, 30);
- Alcohol consumption: evaluated by alcohol consumption status - non-drinkers (person who abstains from alcohol beverages or had less than 12 drinks in lifetime), former drinkers (person who had at least 12 drinks in any one year in lifetime, but no drinks for at least the last 12 months), and current drinkers (person who had at least 12 drinks in the past years and is currently drinking over the past year); and amount in grams consumed per day (separated by gender: male, < 30 g/d, ≥ 30 g/d; female, < 20 g/d, ≥ 20 g/d). We converted reported alcohol intake into an average of pure alcohol in g/d using the midpoints (mean or median) of reported drinking per participants. As standard drinks vary by country, we harmonized records of alcohol consumption using a conversion of 1 unit = 10 g of pure alcohol, as has been used by the European Association for the Study of the Liver (EASL) (31). The grams of alcohol content of the different types of beverage was calculated using the Dietary Guidelines for Americans (32). Although alcohol is a recognized carcinogen, no threshold level of consumption exists for the risk of cancer. Therefore, for practical issues, we used the EASL recommended dose of safe limit alcohol consumption (in g/d) associated with liver injury (31);
- Physical activity: classified as sedentary or active, if individuals engaged < or ≥ 150 minutes per week of moderate-intensity physical activity, respectively (33);
- Family history of CRC: assessed by the absence or presence and, if present, classified by the degree, the number and the age at diagnosis of CRC of the relative (s) (34);

- Diabetes mellitus: defined as fasting glucose ≥ 126 mg/dL, or the 2 h plasma glucose value of ≥ 200 mg/dL during a 75-g OGTT, or glycated hemoglobin (A1c) ≥ 6.5% in two separated samples and/or current use of antidiabetic treatment (35);
- Use of metformin and ASA;
- Body mass index (BMI): separated in 3 categories: eutrophic, BMI < 25 kg/m^2, overweight, BMI 25-29.9 kg/m^2, and obese, BMI ≥ 30 kg/m^2;
- Presence of acanthosis nigricans (yes or no) and presence of ≥ 3 skin tags (acrochordons) on physical examination (36).

Colonoscopies were performed at more than one center and by more than one physician. It was considered positive when any type of polyps and/or cancer was found and negative in those patients without lesions. Patients were classified according to the histological classification of their colonic lesions: non-neoplastic (normal, hyperplastic polyps, inflammatory polyps); non-advanced adenomas; advanced adenoma (≥ 10 mm diameter, ≥ 25% villous component or high-grade dysplasia); CRC (37, 38). Patients with multiple lesions were classified according to the most advanced histology.

It is important to mention that as a routine in our service we request a colonoscopic at the diagnostic of acromegaly and, if this initial examination and the IGF-I levels are normal, we maintain surveillance exams every 10 years. If IGF-I levels remain persistently high, we evaluate a new colonoscopy every 5 years and if there is any abnormality in the previous colonoscopy, a new exam will be repeated between 3 and 10 years, depending on the alteration (number, size, histopathological finding of the lesion).

Hormone assays

All blood samples were collected in the early morning after an 8h fasting period. As this was a retrospective study, the hormonal assessment of acromegaly was collected over decades and, therefore, the immunoassay method varied between the period of disease diagnosis and the end of the study. IGF-I values were reported as times the upper limit of normal (ULN) for the respective patient's age.

Ethics approval

This study was approved by the Ethics Committee of HUCFF/UFRJ and UFRJ Medical School and all patients signed written informed consent forms (number: 44560621.0.0000.5257).

Statistical analysis

Results are presented as frequencies and percentages for categorical variables and as mean ± standard deviation (SD) or median (minimum – maximum) for numerical variables depending on the sample distribution. Mann-Whitney test, Student`s t-test or Kruskal-Wallis test were used to analyze numerical variable, as appropriate. Fisher's exact test and Chi-square test were used to analyze categorical data. Statistical analyses were performed using SPSS 20.0 for Mac (IBM, Chicago, IL, USA). A *p*-value of < 0.05 was considered statistically significant.

Results

Demographic, clinical, and radiological characteristics

Of a total of 277 patients followed at the outpatient clinic, the study included 123 (77 women; 46 men), respecting the pre-established inclusion criteria. The mean (SD) age at diagnosis of acromegaly was 43.1 (± 13.4) years old and mean follow-up time was 13.7 (± 6.8) years. Of the 123 patients, 80 (65%) were considered cured or controlled (for a mean time of 6.8 ± 4.3 years), 28 (22.8%) had active disease, and 15 (12.2%) had discordant levels of GH and IGF-I at the moment of evaluation. Acromegaly was defined as cured or controlled using the current guidelines recommendations (5). As assessed by magnetic resonance imaging, acromegaly was due to a pituitary GH-secreting microadenoma in 8.9% or macroadenoma in 91.1% of the cases. Clinical, laboratory and baseline colonoscopy characteristics of the entire cohort are described in **Table 1**.

Table 1: Clinical, laboratory and colonoscopy characteristics of the patients.

Characteristics	Value
Sex, n (%)	**F: 77 (62.6%) / M: 46 (37.4%)**
Age at diagnosis, years, mean (SD)	**43.1 (13.4)**
Age at baseline colonoscopy, years, mean (SD)	**48.1 (13.5)**
Age at time of evaluation, years, mean (SD)	**56.6 (13.8)**
Follow-up time, years, mean (SD)[1]	**13.7 (6.8)**
Disease duration, years, mean (SD)	**16.5 (7.9)**
Disease activity, years, median (minimum – maximum)	**12 (12 – 32)**
Laboratory at diagnosis: **GH, ng/mL, median (minimum – maximum)** **IGF-I, x ULN, median (minimum – maximum)**	 **16.6 (0.7 – 252)** **3.0 (0.8 – 7.3)**
Laboratory at the time of evaluation: **GH, ng/mL, median (minimum – maximum)** **IGF-I, x ULN, median (minimum – maximum)**	 **0.8 (0.1 – 35)** **0.9 (0.2 – 6.4)**
Disease activity status at time of evaluation: **Cured/ controlled, n (%)** **Uncontrolled, n (%)** **Discordant levels of GH and IGF-I, n (%)**	 **80 (65%)** **28 (22.8%)** **15 (12.2%)**

Disease activity time until first colonoscopy, years, median (minimum – maximum)	**9 (1 – 27)**
Smoking status:	
Non-smokers, n (%)	**92 (74.8%)**
Current smokers, n (%)	**8 (6.5%)**
Former smokers, n (%)	**23 (18.7%)**
Smoking load:	
< 20 pack-years, n (%)	**105 (85.4%)**
≥ 20 pack-years, n (%)	**18 (14.6%)**
Alcohol:	
Non-drinkers, n (%)	**93 (75.6%)**
Current drinkers, n (%)	**21 (17.1%)**
Former drinkers, n (%)	**9 (7.3%)**
Alcohol load:	
< 20 g/d (F) and/or < 30 g/d (M), n (%)	**110 (89.4%)**
≥ 20 g/d (F) and/or ≥ 30 g/d (M), n (%)	**13 (10.6%)**
Physical activity:	
Sedentary, n (%)	**92 (74.8%)**
Active, n (%)	**31 (25.2%)**
Family history of CRC, n (%)	**23 (18.7%)**
First degree relative with CRC, n (%)	**9 (39.1%)**
BMI:	

Eutrophic, n (%)	**15 (12.3%)**
Overweight, n (%)	**44 (36.1%)**
Obesity, n (%)	**63 (51.6%)**
Acrochordons, n (%)	**17 (13.8%)**
≥ 3, n (%)	**12 (70.6%)**
Acanthosis nigricans, n (%)	**15 (12.2%)**
Diabetes mellitus, n (%)	**70 (56.9%)**
Use of metformin, n (%)	**62 (50.4%)**
Use of ASA, n (%)	**8 (6.5%)**
Baseline colonoscopy:	
Non-neoplastic, n (%)	**99 (80.5%)**
Non-advanced adenomas, n (%)	**18 (14.6%)**
Advanced adenomas, n (%)	**4 (3.3%)**
CRC, n (%)	**2 (1.6%)**

SD: standard deviation; F: female; M: male; GH: growth hormone; IGF-I: insulin-like growth factor type I; ULN: upper limit of normal; CRC: colorectal cancer; BMI: body mass index; ASA: acetylsalicylic acid.

[1] Follow-up time: time from acromegaly diagnosis to death or end of the study (August 31, 2022).

Colonoscopy results

All colonoscopies included had a satisfactory colonic preparation, associated with a good quality of the exam with cecal intubation, respecting the inclusion criteria. The median time interval between the diagnosis of acromegaly and the baseline colonoscopy was 5 years. The histopathological findings of the baseline colonoscopy of each patient were: non-neoplastic in 99 (80.5%) patients, non-advanced adenomatous polyps in 18 (14.6%), advanced adenomatous polyps in 4 (3.3%), and CRC in 2 (1.6%). Regarding these colonoscopies characterized as non-neoplastic, 65.3% were normal, and 34.7% had a hyperplastic or inflammatory polyp. Polyps were located most often in the sigmoid colon and rectum (51.9%), and 68.2% of the baseline colonoscopies had polyps measured

≤ 5 mm, 20.4% measured between 6-9 mm, and 11.4% were ≥ 10 mm. Regarding age at baseline colonoscopy, 54 (43.9%) were individuals < 45 years old, 16 (13%) were between 45 – 49 years, and 53 (43.1%) were ≥ 50 years. Of the younger patients (< 45 years), only 3 had non-advanced adenomas and none had advanced adenomas and/or CRC. Of those between 45 – 49 years, 2 had colonoscopy with non-advanced adenomatous polyps, 1 with advanced adenomatous polyps and none with CRC. And among individuals with ≥ 50 years, 13 had non-advanced adenomas, 3 advanced adenomas, and 2 CCR. During follow-up, at least 53 (43.1%) patients underwent surveillance colonoscopies, and at the end of the study, another patient was diagnosed with CRC, totalizing 3 (2.4%) patients with this neoplasia.

Comparison of risk factors between patients with non-neoplastic vs adenomatous polyps plus CRC

When we separate the findings of the baseline colonoscopy into 2 groups: non-neoplastic vs adenomatous polyps (non-advanced and advanced) plus CRC and analyzed possible correlations with the proposed clinical and biochemical variables, smoking, age at diagnosis of acromegaly and age at the time of this colonoscopy showed a statistically significant difference between the groups. While 45.8% of the patients with an adenomatous polyp and CRC were smokers and former smokers, only 20.2% of patients with a non-neoplastic colonoscopy were smokers and former smokers (p = 0.026). The mean age at diagnostic of acromegaly in those with a non-neoplastic exam was 40.9 (± 13.3) years, while those with adenomas and CRC were 51.7 (± 10.4) years (p < 0.001). And the mean age of the patients at the time of the baseline colonoscopy was 46.1 (± 13.7) years in those with non-neoplastic findings and 55.6 (± 9.2) years in those with pre-malignant/ malignant lesions (p = 0.002) (**Table 2**).

Table 2: Analysis of the clinical and laboratory population characteristics dividing the baseline colonoscopy into 2 groups: non-neoplastic and adenomatous polyps (non-advanced and advanced adenomatous polyps) plus CRC.

	Non-neoplastic	**Adenomatous polyp + CRC**	***P*-value**
Sex, n (F:M) (%)	**61:37 (62.2:37.8)**	**15:9 (62.5:37.5)**	**0.982**
Age at diagnostic, years, mean (SD)	**40.9 (13.3)**	**51.7 (10.4)**	**< 0.001**
Age at baseline colonoscopy, years, mean (SD)	**46.1 (13.7)**	**55.6 (9.2)**	**0.002**
Disease activity status at baseline colonoscopy, n (%):			**0.527**
Cured/ controlled	**78 (78.8)**	**20 (83.3)**	
Uncontrolled	**16 (16.2)**	**4 (16.7)**	
Discordant	**5 (5)**	**0 (0)**	
Laboratory at diagnosis:			
GH, ng/mL, median (minimum – maximum)	**18.8 (0.65 – 252)**	**12.6 (1.13 – 169)**	**0.182**
IGF-I, x ULN, median (minimum – maximum)	**2.98 (1 – 7)**	**3.53 (1 – 7)**	**0.392**
Alcohol consumption, n (%):			
Non-drinkers	**74 (74.7)**	**19 (79.2)**	**0.787**
Current drinkers	**18 (18.2)**	**3 (12.5)**	
Former drinkers	**7 (7.1)**	**2 (8.3)**	
Alcohol load, n (%):			

<20 g/d (F) and/or < 30 g/d (H)	**88 (88.9%)**	**22 (91.7%)**	**0.682**
≥20 g/d (F) and/or ≥30g/d (H)	**11 (11.1%)**	**2 (8.3%)**	
Smoke status, n (%):			
Non-smokers	**79 (79.8)**	**13 (54.2)**	**0.026**
Current smokers	**6 (6.1)**	**2 (8.3)**	
Former smokers	**14 (14.1)**	**9 (37.5)**	
Smoking load, n (%):			
< 20 pack-years, n (%)	**86 (86.9)**	**19 (79.2)**	**0.351**
≥ 20 pack-years, n (%)	**13 (13.1)**	**5 (20.8)**	
Physical activity, n (%):			
Sedentary	**71 (71.7)**	**21 (87.5)**	**0.105**
Active	**28 (28.3)**	**3 (12.5)**	
Family history of CRC, n (%):			
No	**80 (80.8)**	**20 (83.3)**	**0.846**
Yes	**19 (19.2)**	**4 (16.7)**	
Diabetes, n (%)	**57 (57.6)**	**13 (54.2)**	**0.723**
BMI, n (%):			
Eutrophic	**11 (11.2)**	**4 (16.7)**	**0.706**
Overweight	**35 (35.7)**	**9 (37.5)**	
Obesity	**52 (53.1)**	**11 (45.8)**	
Acrochordons, n (%):			
No	**85 (85.9)**	**21 (87.5)**	**0.821**
Yes	**14 (14.1)**	**3 (12.5)**	
≥ 3	**9 (9.1)**	**3 (12.5)**	**0.218**

Acanthosis nigricans, n (%)	**12 (12.1)**	**3 (12.5)**	**0.973**
Use of metformin, n (%)	**50 (50.5)**	**12 (50)**	**0.929**
Use of ASA, n (%)	**6 (6.1)**	**2 (8.3)**	**0.695**

SD: standard deviation; F: female; M: male; GH: growth hormone; IGF-I: insulin-like growth factor type I; ULN: upper limit of normal; CRC: colorectal cancer; BMI: body mass index; ASA: acetylsalicylic acid.

Subsequent colonoscopies

Some patients included in the study had undergone colonoscopy surveillance throughout their clinical follow-up, and of these: fifty-three patients underwent a second colonoscopy, ten a third, two a fourth, two a fifth, and one a sixth exam. In the evaluation of subsequent colonoscopies in those patients with a worse histopathological finding over time (for example, non-neoplastic pattern progressing to adenomatous polyps, or non-advanced adenomatous polyps to advanced histopathological findings or CRC), no variable demonstrated a significantly difference between patients with no change in the colonoscopy and those that showed any progression.

The characteristics of the 3 patients in our cohort diagnosed with CRC are presented in **Table 3**.

Table 3: Clinical and biochemical characteristics of patients diagnosed with CRC in our cohort.

Characteristics	Patient 1	Patient 2	Patient 3
Sex (F/ M)	**F**	**M**	**F**
Age at acromegaly diagnosis, years	**67**	**50**	**51**
Age at the time of evaluation, years	**86**	**74**	**66**
Age at CRC diagnosis, years	**77**	**55**	**55**
Disease activity status at the diagnosis of CRC	**Cured/ controlled**	**Uncontrolled**	**Uncontrolled**
Disease activity status at the time of evaluation	**Cured/ controlled**	**Cured/ controlled**	**Cured/ controlled**
Laboratory at diagnosis: **GH, ng/mL** **IGF-I, x ULN**	 **23.6** **1.1 x ULN**	 **22.9** **1.6 x ULN**	 **1.69** **1.5 x ULN**
Laboratory at time of evaluation: **GH, ng/mL** **IGF-I, x ULN**	 **0.8** **0.7 x ULN**	 ***** **0.6 x ULN**	 **0.6** **0.8 x ULN**
Alcohol consumption	**Non-drinker**	**Non-drinker**	**Non-drinker**
Smoke status	**Non-smoker**	**Non-smoker**	**Former smoker**
Physical activity	**Sedentary**	**Sedentary**	**Sedentary**
Family history of CRC	**No**	**Yes (5 relatives, 3 of which are first degree)**	**No**
Diabetes	**Yes**	**Yes**	**Yes**

BMI	Obesity	Overweight	Obesity
Acrochordons	**No**	**No**	**No**
Acanthosis nigricans	**No**	**No**	**No**
Use of metformin	**Yes**	**Yes**	**Yes**
Use of ASA	**Yes**	**No**	**No**

F: female; M: male; GH: growth hormone; IGF-I: insulin-like growth factor type I; ULN: upper limit of normal; CRC: colorectal cancer; BMI: body mass index; ASA: acetylsalicylic acid.

** Patient 2 was under medical treatment with pegvisomant, therefore his biochemical follow-up involved only IGF-I level measurement.*

Discussion

The main cause of death in patients with acromegaly has shifted from cardiovascular disease to cancer in the past decades (7, 8). This may be a reflex of the treatment progress made in recently years, decreasing the mortality, and increasing the cure and disease control rates, when compared with older studies (8, 39). This decrease in overall mortality and consequent increase in life expectancy, results in an expected increase in the incidence of relevant age-dependent diseases, such as CRC.

In Brazil, the main cause of death in the general population in 2020 was cardiovascular disease, followed by infectious disease, and then cancer (40). Excluding non-melanoma skin tumors, CRC in Brazil is the third most incident neoplasm in both genders, whereas in the United States, CRC ranks the third in both new cases of cancer and in cause of cancer mortality for both men and women, and in Europe it ranks third in new cases of cancer and second in cancer mortality for both genders (41-44). It is estimated in the Brazilian population for the period of 2023-2025, 45,630 new cases of CRC, corresponding to an estimated risk of 21.1 cases/ 100,000 inhabitants, with 21,970 cases in men and 23,660 cases in women (44). These values correspond to an estimated risk of 20.78 new cases per 100,000 men, and 21.41 per 100,000 women (44).

There is a large amount of evidence that GH and IGF-I promote cell proliferation, angiogenesis, and growth, besides suppressing DNA damage repair pathways and apoptosis, what could therefore be involved in tumor promotion and progression (2). The reported prevalence of colorectal neoplasia in patients with acromegaly in nationwide studies has ranged from 0.3% to 1.9% (11, 12, 45-48).

Although most authorities currently accept that acromegaly is associated with an increased risk of developing CRC, the magnitude of such risk continues to be a matter of debate (49).

In our data, we were unable to show any direct correlation between the presence of colonic adenomatous polyps or carcinoma and disease activity, or any correlation with individual levels of GH and IGF-I at diagnosis. This result is in contrary to several studies that consistently suggest that IGF-I levels above ULN (but not always GH levels) are significantly related to the prevalence of polyps in acromegaly (50-52). Anecdotally, our patients with CRC had a slightly increased IGF-I levels at diagnosis. This data should be evaluated with caution, as during our follow-up, only 3 patients were diagnosed with CRC, which represents a small sample to appraise, which probably explains this result. Another relevant data resides in the significant follow-up of the cohort, mean of 13.7 years (with a maximum time of 31 years) and, besides this, only one more case of CRC was diagnosed during the study (beyond the two at baseline colonoscopy).

When evaluating the modifiable risk factors for CRC in our patients with acromegaly, only the smoking status was shown to be statistically significant, in relation to the risk of developing adenomatous polyps and CRC. This finding corroborates with the literature, since tobacco smoking is an important factor favoring the development of colonic polyps and CRC (18). Assessing the general population and compared to non-smokers, current smokers have an apparent increased risk of adenomatous polyps (RR, 1.29, 95% CI, 1.11 – 1.49) and CRC (RR, 1.07, 95% CI, 0.99 – 1.16), as well as former smokers have also an increased risk for adenomas (RR, 1.18, 95% CI, 1.05 – 1.32) and CRC (RR, 1.17, 95% CI, 1.11 – 1.12) (18, 53).

Alcohol consumption is a risk factors for many types of cancer, including CRC (54). Although some issues remained in debate, such as de dose-risk relation of alcohol intake with this neoplasm, meta-analysis indicate that when compared to nondrinkers or occasional drinkers, moderate drinking (12.6 – 49.9 g/d of ethanol) and heavy drinking (≥ 50 g/d of ethanol) are associated with an increased risk do CRC of 21% (RR 1.21, 95% CI, 0.95 – 1.05) and 52% (RR 1.52, 95% CI, 1.27-1.81), respectively (19). However, in our study, we found no difference between the drinking status or the ethyl load of the patients and the colonoscopy results (non-neoplastic vs adenomatous polyps and CCR; risk of new colonic lesion during follow-up), which might be explained by the large percentage (75.6%) of non-drinkers patients in the cohort.

Obesity and diabetes are conditions associated with an increased prevalence of CRC in the general population, reflecting the hypothesis of insulin resistance and, consequently, hyperinsulinemia and an increase in proinflammatory cytokines in CRC tumorigenesis (55, 56). Furthermore, colon tissue has insulin receptors, and insulin stimulates the growth of both normal and CCR cells *in vitro* and in animal

studies (55, 57). Patients with acromegaly have an increased prevalence of insulin resistance generating hyperinsulinemia (1). Although some previous studies point to a relationship between high insulin levels and a higher risk of colonic lesions in the population with acromegaly (58, 59), others do not support this finding (60), reflecting inconsistency. Nevertheless, type 2 diabetes mellitus has been shown to consistently increase CRC risk in the non-acromegaly patients (21), but some observational studies have reported no difference in the relationship between the frequency of diabetes and colonic lesion in acromegaly (61, 62).

Evaluating BMI and acromegaly can be difficult, since these patients may present a higher BMI related to an increase in lean body mass. Although the link between an increased BMI and CRC risk in general population is statistically robust in the literature (63), previous studies have not demonstrated a direct association of BMI and the presence of colonic polyps or cancer in patients with acromegaly (61, 62). In our study population, the presence of diabetes mellitus, overweight/obesity, and acanthosis nigricans (an indirect sign of insulin resistance and hyperinsulinemia) were not associated with a higher risk of developing adenomas or CRC.

In the general population, acrochordons (also known as skin tags) are very common benign connective tissue tumors of the dermis, which are also associated with acromegaly (36). Some authors have suggested that there is a relationship between acrochordons and colon polyps, although the physiopathological mechanism of this relation were not well elucidated (64). Nevertheless, hyperinsulinemia apparently plays an important role in the development of the skin tags, as well as in the appearance of colonic polyps (65). Insulin activates IGF-I receptors and epidermal growth factor receptors in cells, such as keratinocytes and fibroblasts, inducing their proliferation (65, 66). Previous studies demonstrated a higher risk of colonic adenomas in patients with acromegaly who had ≥ 3 skin tags (36). However, there are also studies indicating no relationship between them (12, 62). In line with these last studies, our series did not demonstrate a relationship between skin tags and any colonic lesion found.

A substantial body of evidence demonstrated that increased levels of physical activity are associated with a reduced risk of CRC, estimating a reduction by one-fourth to one-third for the most physically active populations as compared to the least active (23, 67). The clear mechanism to explain this still remains to be elucidated, but it may involve the decreased inflammation, increased insulin sensitivity, and consequent decrease in insulin levels (67). Most of our patients were sedentary (74.8%) and this may be a reason why physical activity did not prove to be a statistically significant factor in reducing the risk of developing adenomatous polyps and/or CRC in the initial exam or in subsequent ones.

Still in the issue of preventive factors against CRC, evidence points out that metformin may have an anticancer role in patients with diabetes and insulin resistance (25, 68). The mechanism of metformin antitumoral activity is not fully understood, but its action in reducing insulin levels and inhibiting phosphorylation of IGF-I receptor/ insulin receptor and its pathways inhibition of cell proliferation and growth, as well as inducing apoptosis, have an important role (69, 70). Aspirin has also been associated to a reduced risk of CRC (71). Its chemoprotective effect has been attributed to its capacity of inhibiting the cyclooxygenase (COX), the enzyme responsible for the synthesis of prostaglandins. COX, in particular the isoform COX-2, has been described to be abnormally expressed in cancer cell lines and has been involved in the process of perpetuate pro-inflammatory signals, which promote cellular proliferation, angiogenesis, and apoptotic resistance (24, 71). The use of both medications among the study participants did not demonstrate a protective role against polyps or CRC.

When we evaluate the nonmodifiable risk factors, CRC and colonic adenomas are more common in men than women (16). Despite differences in tumor location (women have a higher risk of developing proximal colon cancer) and mortality (inferior in females), none of the major organizations recommends that screening be stratified by sex (72). Regardless of the slight predominance of females in our patients with acromegaly (62.6%), gender was not a risk factor for adenomatous polyps and/or CRC, when compared to non-neoplastic colonoscopies in the baseline exam (p = 0.982), neither in the relation to the risk of progression to adenoma or CRC during colonoscopy surveillance at follow-up (p = 0.517).

People with family history of CRC, even in its sporadic form unrelated to high-risk genetic disorders (such as familial adenomatous polyposis or Lynch syndrome) have a higher personal risk for developing this disease, what represents a modifier of the screening strategy for all CRC guidelines. In these cases, it is recommended to start screening at 40 years old or 10 years before the youngest case in family (whichever comes first) (73). The greater the number of affected relatives, the degree of kinship, and the younger the age at diagnosis of CRC of the family member, the greater the personal risk of the individual (34). When we evaluated the presence of CRC family history in our population, there was no statistical difference between the analyses of the histopathological findings related to the colonoscopies, either when dividing the findings of the first exam into non-neoplastic *vs* adenomatous polyps and CRC, or when analyzing the evolutionary worsening of the colonoscopies surveillance follow-up. Although the prevalence of first-degree relatives with a positive family history of CRC in our patients (7.3%) correspond to that found in various studies in control groups in the general population (4-10%), no difference was found, possibly due to the small size of the evaluated sample. It is noteworthy that among the 3 patients with CRC in our cohort, one of them had a strong positive family history, with 5 relatives also diagnosed with this neoplasm (3 of them of first degree), and three

diagnosed before age 50, which would probably classify them as having Lynch Syndrome, according to the Amsterdam II criteria (74). The fact that one of our three patients diagnosed with CRC during follow-up probably had a genetic syndrome related to this neoplasm points to a higher risk of this syndrome than the role of acromegaly as a significant risk factor.

The incidence of CRC is strongly age related and continues to rise with increasing age, which resulted in the recommendation to start screening at age 50 years in average-risk persons by the gastroenterology, oncology, and endoscopy societies for decades (73, 75, 76). Although the absolute risk of developing CRC is lower in adults younger than 50 years, recent analyzes indicate a trend of decreasing incidence and mortality rates in people ≥ 50 years, and an increasing risk in cohorts of adults younger than that age (77, 78). This fact has prompted at least two groups to lower the recommended age of first screening: in 2018, the American Cancer Society issued a qualified recommendation to initiate screening in individuals at average risk of CRC at age 45 years; in 2021, the United States Preventive Services Task Force changed its recommendation to include screening for CRC in adults starting at age 45 as a GRADE B (78, 79). We found that the greater the age at the diagnosis of acromegaly and at the moment of the colonoscopy, the greater the risk for the appearance of a colonic premalignant/malignant lesion at the baseline exam. This data corroborates the known fact of the directly proportional risk of polyps and CRC and the aging of the individual.

Epidemiological studies indicate that there are minor differences in risk of adenomas based on race and ethnicity, although American publications demonstrate a particular higher risk of advanced adenomas and adenomas in the proximal colon in African Americans than in the Caucasian population (80-82). In our study, we chose not to evaluate the ethnicity as one of the risk factor variables, since race and ethnicity are difficult to assess in a population as mixed in this regard as the Brazilian.

Evaluating the factors associated with a higher risk for CRC, a relevant point in our study correspond to the age variable. Despite the rather heterogeneous data in the literature regarding the degree of risk of CRC in acromegaly, societies and specialists in endocrinology recommend in their guidelines the first screening for this neoplasm at the time of acromegaly diagnosis, regardless of the individual's age (5, 26, 27). Our study shows that individuals with higher risk were the oldest (aged over 50 years). Colonoscopy is an invasive procedure, with potential harmful that may be enhanced in acromegaly patients, such as polypectomy bleeding (more common in proximal colon – 25-40% of polyps and 50% of adenocarcinomas in acromegaly are located in the ascending and transverse colon), perforation (increased in the presence of diverticular disease – increased in acromegaly), and cardiopulmonary complications (arrhythmias, hypotension, oxygen desaturation) (2, 83). In addition, there are specific technical difficulties in

this population: standard bowel preparation could lead to suboptimal results, because intestinal transit is slower than normal subjects; the colon length and circumference are often increased (dolichocolon with megacolon), making complete intubation and identification of minor lesions more difficult (84-86). Therefore, perhaps CRC should be included within the same screening recommendations for other neoplasms (such as prostate and breast cancer) (27), that is, we should maintain the level of recommendation (and age of first screening) equal to the general population, as data in the literature does not support acromegaly as a high risk factor for CRC that would justify a change in the recommendation of the age of initial colonoscopy.

We must acknowledge some limitations of our study: (1) acromegaly is a rare disease and although 123 patients is a relevant sample in this context, this is a relatively small number of patients when we propose to evaluate the CRC risk factors; (2) there is no matched control group for comparison purposes; (3) this was a retrospective analysis, and for that reason it may not be possible to avoid selectivity bias; (4) although only full-length good standard colonoscopies were included, they were not performed in a single center, therefore substances used to bowel preparation, endoscope model and expertise of endoscopist could vary between centers; (5) the study encompassed the laboratory assessment of acromegaly hormonal control over several decades, therefore immunoassay methods varied between the period of the disease diagnosis and the end of the study, making comparison difficult.

Conclusion

Smoking and advanced age were the variables that were different in those patients developing adenomatous polyps and/or CRC in our study, among the risk factors classically related to this neoplasm. Among these factors, age, specifically over 50 years, proved to be the most robust risk factor for adenomatous polyps and CRC, which corroborates the data found in the general population. More nationwide and multicentric studies are urgently needed on this subject, in order to assess the real magnitude risk of acromegaly as an individual risk for CRC, but our data suggests that the age of initial CRC screening in acromegaly could be revised.

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4- Considerações finais

Evidências atuais apontam que pacientes com acromegalia possuem um maior risco (leve a moderado) de desenvolver CCR quando comparado à população geral, embora os dados sobre o assunto não sejam homogêneos e os estudos que abordam este tema tenham alguns vieses e limitações em suas interpretações. Desta forma, a acromegalia provavelmente deveria ser incorporada no grupo de fatores de risco menores associados ao CCR, como: tabagismo, etilismo, obesidade, diabetes, sedentarismo, dentre outros.

Nosso estudo demonstrou que os pacientes com acromegalia que desenvolveram pólipos colônicos adenomatosos e/ou CCR possuíam idade mais avançada, mesmo quando associado a outros fatores de risco para esta neoplasia. Como é demonstrado na literatura, os fatores mais relevantes ao surgimento de CCR em sua forma esporádica (e modificadores nas recomendações de rastreio) são: idade e história familiar da neoplasia.

Portanto, talvez o rastreio de CCR nestes indivíduos deva seguir as mesmas recomendações preconizadas para a população geral, ao invés de ser iniciada no momento do diagnóstico da acromegalia, ou seja, diferente do que atualmente é sugerido pelas diretrizes das sociedades endocrinológicas. Contudo, a fim de revermos as recomendações atuais, permanece imperativo estudos futuros com maior casuística sobre o tema, especialmente estudos multicêntricos nacionais ou de grandes bancos de dados populacionais.

5- Conclusões

- A acromegalia está associada a um maior risco de alterações ao exame de colonoscopia, sendo que 17,9% dos nossos pacientes apresentaram pólipos adenomatosos (avançados e não avançados) e 1,6% CCR no exame de base. Ao longo do acompanhamento, outro caso de CCR foi diagnosticado, totalizando 2,4% casos de CCR em nossa coorte de 123 pacientes.
- Dentre os fatores de risco para desenvolvimento de lesões colônicas (pré-malignas e malignas), aqueles que demonstraram significância estatística com relação ao surgimento de pólipos adenomatosos e/ou CCR foram: tabagismo e idade mais avançada ao diagnóstico da acromegalia e no momento da realização da colonoscopia de base.
- Em congruência com o que é consagrado na literatura para a população geral, a idade ≥ 50 anos representou o fator de risco mais robusto e a atividade da doença não se associou a maior risco de adenomas e/ou CCR. Nossos dados sugerem que a idade para rastreio desta neoplasia na acromegalia deva ser revisada.

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7- Anexo I

Avaliação dos fatores de risco para neoplasia intestinal na Acromegalia

Nome:_____.

Sexo:_____.

Data de nascimento:_____.

Telefone(s):_____.

Prontuário:_____.

1. Avaliação das características clínicas e bioquímicas:

- Quando foi o diagnóstico de Acromegalia?_____.
- Quando iniciou a clínica (sinais/ sintomas) da Acromegalia?_____.
- Qual o tratamento proposto?
  ( ) cirurgia ( ) medicamentoso ( ) radioterapia
- Se medicamentoso, qual (is) (dose/ tempo de uso)? _____.
- Valor GH ao diagnóstico: _____.
- Valor IGF-I ao diagnóstico: _____. VR: _____.
- Valor GH no momento da avaliação: _____.
- Valor IGF-I no momento da avaliação: _____. VR: _____.
- Tempo total de doença: _____.
- Tamanho tumoral antes de qualquer tratamento (cm): _____.
- Acromegalia curada/ controlada: ( ) sim ( ) não
- Data controle / Tempo de cura/controle? _____.
- Quanto tempo entre o diagnóstico e o controle/cura (atividade de doença):

  _____.
- Tempo total de seguimento no ambulatório: _____.
- O senhor (a) fuma ou já fumou? ( ) sim ( ) não
- Se sim, qual a caga tabágica? _____maços-ano.
- Se ex-tabagista, quando parou? _____.
- O senhor (a) ingere álcool? ( ) sim ( ) não

- Carga álcool: _____ g/dia.
- Se ex-etilista, quando parou? _____.
- Pratica atividade física? ( ) sim ( ) não
- Se sim, qual a frequência? _____min/sem.
- Há alguém na família com câncer colorretal? ( ) sim ( ) não
- Se sim, quantos, qual o grau de parentesco e a idade ao diagnóstico? _____.
- O senhor (a) tem Diabetes? ( ) sim ( ) não
- Se sim, faz uso de metformina? ( ) sim ( ) não
- O senhor (a) faz uso de AAS? ( ) sim ( ) não
- Exame físico:
- Peso: _____ kg
- Altura: _____ cm
- IMC: _____ kg/cm^2

( ) Acantose Nigricans

( ) Acrocórdons -> Quantidade: _____.

2. Avaliação das características da colonoscopia:

- Data: _____.
- Laudo: _____.
- Histopatológico:_____.
- HUCFF: ( ) Extra HUCFF: ( )

8- Anexo II: Outros artigos publicados

Endocrine CONNECTIONS | B Maia *et al.* | New acromegaly treatments | 9:12 | R274–R285

REVIEW

Novel therapies for acromegaly

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Abstract

Acromegaly is a systemic disease associated with increased morbidity and mortality. Most of these comorbidities can be prevented or delayed with adequate disease treatment. Although three modalities of treatment (surgery, medical treatment, and radiotherapy) are available and new drugs were approved in the last decades, there are still some patients that maintain disease activity despite treatment. Therefore, there is a need for novel therapies for acromegaly and for that purpose new formulations of currently used drugs and also new drugs are currently under study. In this review, we summarize the novel therapies for acromegaly.

Key Words

- acromegaly
- novel treatments
- medical treatment
- somatostatin receptor ligands
- oral octreotide

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Introduction

Acromegaly is a chronic systemic rare disease most commonly caused by a somatotroph pituitary adenoma with autonomous overproduction of growth hormone (GH) and a consequent increase in insulin-like growth factor type I (IGF-I) levels produced mainly by the liver (1). Clinical manifestations include somatotrophic effects (acral enlargement, facial alterations, arthralgia), cardiovascular, respiratory, metabolic complications and a possible increase in some neoplasias (2). If left untreated, acromegaly results in an increased morbi-mortality with a significant decrease in quality of life and an average 10-year reduction in life expectancy (3, 4, 5). Disease control by reducing GH to <1 µg/L and normalizing IGF-I restores mortality to normal rates of the general population (2, 4). In addition to biochemical control, treatment aims to prevent tumor growth or, ideally, induce tumor shrinkage. Currently, treatment of acromegaly includes neurosurgery, medical therapy and radiotherapy (4, 6, 7).

Current treatments

Surgical treatment

Surgery is the gold standard treatment of acromegaly since it represents the only therapy capable of rapidly curing acromegaly (4). With experienced pituitary surgeon, transsphenoidal surgery results in a remission rate of approximately 85% for microadenomas and 40–60% for macroadenomas (8, 9). Several factors are predictors of surgical success: tumor size and invasiveness, preoperative GH level, patient's gender and the surgeon's experience (10, 11, 12).

Medical treatment

Medical treatment plays an important role in acromegaly as an adjuvant therapy, since surgical cure is achieved in a fraction of patients, or as primary therapy, since few patients have clinical contraindications or refuse to be submitted to surgery (4, 10). Currently, there are

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Table 1 Currently approved medical therapies for acromegaly.

Drug	Mechanism of action	Dosage	Biochemical efficacy (%)	Effect on tumor mass	Main side effects
Octreotide long-acting release (4, 14)	Somatostatin receptor ligand (higher SST2 affinity)	10–40 mg/month, IM	30–40	Tumor shrinkage (66%)	Gastrointestinal, injection-site reactions
Lanreotide autogel (4, 14)	Somatostatin receptor ligand (higher SST2 affinity)	60–120 mg/month, deep SC	30–40	Tumor shrinkage (62.9%)	Gastrointestinal, injection-site reactions
Pasireotide (4, 18, 62)	Somatostatin receptor ligand (higher SST5 affinity)	40–60 mg/month, SC	54	Tumor shrinkage (80%)	Hyperglycemia, gastrointestinal, injection-site reactions
Cabergoline (4, 22, 26)	Dopamine receptor agonist	1.5–3.5 mg/week, PO (by mouth)	18	Tumor shrinkage (33%)	Gastrointestinal, nasal congestion, fatigue, orthostasis, headache, cardiac valve abnormalities
Pegvisomant (4, 24)	GHR antagonist	10–40 mg/day, SC	70	No effect	Injection-site reactions, elevated liver enzymes

GHR, growth hormone receptor; IM, intramuscular; SC, subcutaneous; SST, somatostatin receptor.

three classes available for the treatment of acromegaly: somatostatin receptor ligands (SRLs), dopamine agonists, and GH receptor antagonist (4, 7, 10) (Table 1).

Somatostatin receptor ligands

Somatostatin receptor ligands are the most frequently prescribed therapy and there are three different available drugs in this class, divided into two generations: first-generation SRLs (fg-SRLs), represented by octreotide long-acting release (OCT-LAR) and lanreotide autogel, that are considered first-line therapy; and second-generation SRL, represented by pasireotide (PAS) (13). Both fg-SRLs, in real-life, seem to be equally effective in controlling GH and IGF-I levels in approximately 30–40% of patients (14). In patients well controlled with low dose fg-SRL, extended dose intervals can be tried with the majority of patients maintaining disease control (15). Pasireotide is a multi-somatostatin-receptor ligand with affinity for somatostatin receptors (SST) 1, 2, 3 and mainly to 5. The fg-SRLs preferentially bind to SST2. Pasireotide has been demonstrated to provide superior clinical efficacy over fg-SRLs in both treatment-naïve patients and in those inadequately controlled with fg-SRLs (16, 17). In a real-life study, IGF-I normalization was achieved in 54% of patients with acromegaly that were not controlled with fg-SRLs (18). However, pasireotide may also cause a worsening of glucose homeostasis, a less frequent adverse effect with the use of fg-SRLs (16, 17, 19, 20).

Dopamine agonists

Dopamine agonists, represented by cabergoline, have a modest efficacy in acromegaly and plays a role as adjunctive therapy in cases with mildly elevated IGF-I levels (<2.5 times the upper limit of normal (ULN)) (7, 21, 22). Long-term disease control is observed in 18% for patients in monotherapy (22).

Pegvisomant

Pegvisomant (PEGV) is a selective growth hormone receptor antagonist usually administered as second-line therapy, achieving biochemical control rates of 90% or more in clinical trials (23) and a real-life control rate of approximately 70% (24). Nevertheless, compliance (daily injections), side effects (hepatotoxicity, injection site reactions), inadequate up-titration and not having a tumor-suppressive effect limit its use. Another non-medical factor that limits its use in some countries is the difficulty of access due to cost-effectiveness issues (25).

Combination therapy

As evidenced previously, monotherapy is not able to achieve complete biochemical control in a considerable number of patients in clinical practice, requiring combined drug administration to improve clinical outcomes. In these cases of partial response, combined medical treatment may have the benefit of reducing side effects associated with an individual higher dose medication by decreasing the frequency of injections and/or total drug dose (4, 21). Combinations used in acromegaly treatment are: fg-SRL+cabergoline (allowing disease control in approximately 23% of patients); fg-SRL+PEGV and PEGV+cabergoline that allows disease control in similar rates to PEGV monotherapy, but with additional benefits

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of action in the tumor and allowance of lower PEGV doses (4, 22, 26, 27, 28, 29).

Other drug therapies

In addition to the aforementioned three classes of drugs for the treatment of acromegaly, there are also others medical therapies, reserved in special situations.

Oral estrogens and selective estrogen receptor modulators (SERMs) are capable of reducing IGF-I levels through modulating GH responsiveness, by inducing SOCS2 expression and thereby negatively inhibiting the GHR-JACK2-STAT5 signaling pathway (30). This so-called first-pass effect may be seen in patients with acromegaly when used alone or in combination with an SRL or cabergoline (31). Nevertheless, these medications are not part of the regular acromegaly management arsenal and further studies are necessary to demonstrate their real effectiveness and safety.

Temozolomide is an alkylating agent that induces DNA damage, causing the death of tumor cells (32). It is a chemotherapy reserved for aggressive pituitary tumors and pituitary carcinomas, refractory to the aforementioned conventional therapy (32).

Radiation therapy

Radiation therapy (RT) is usually considered a third-line option, reserved as an adjuvant therapy for patients with aggressive tumors who failed surgical and medical treatment (4, 6). The effects of RT are not immediate and biochemical remission may be achieved only after 5–15 years, requiring the use of drugs in the interim (33). Remission rates of 50–70% have been reported with stereotactic radiotherapy in patients followed up to 15 years (33, 34, 35). The great disadvantage of this method that places it as a last-line therapy is the frequent occurrence of complications, such as hypopituitarism (10–50% of patients within 5–10 years), cognitive changes, radiation-induced cranial nerve damage, cerebrovascular disease, secondary tumors and radionecrosis (33, 34, 35).

Novel therapies

The current clinical management of acromegaly is far from ideal, since biochemical control is not achieved in all patients; adverse events may be critical in some individuals, leading to intolerance and limited use; and except for DA, all frequently used drugs require regular injections, which could reduce the quality of life (36, 37). In recent years, novel therapies have been studied in preclinical and clinical trials, and in the year 2020, one of them was approved for clinical treatment. While some of them correspond to new therapeutic agents, others represent new SRLs with different routes of administration or even a novel combination of already existing drugs (Table 2).

New combination of drugs already approved

Pasireotide and pegvisomant

Pasireotide and PEGV are two of the most effective drugs already used for medical therapy in acromegaly, but their combined treatment has not been extensively studied. Potential benefits of this combination could be a reduction in the PEGV dose, reflecting a reduction in the total cost of treatment; reduction of glucose abnormalities associated with PAS monotherapy; and biochemical control of acromegaly resistant to conventional medical therapy.

The PAPE study is currently the only published trial that aimed to assess efficacy and safety of PAS alone or in combination with PEGV by switching patients with acromegaly who were well controlled with fg-SRLs and PEGV to PAS with or without PEGV (38). It is a 24-week, prospective, single-center, open-label, investigator-initiated study involving 61 well-controlled (defined as an IGF-I ≤1.2× ULN) acromegaly patients that had received weekly PEGV and monthly injections of either OCT-LAR 30 mg or lanreotide autogel 120 mg for at least 6 months prior to study entry. At baseline, fg-SRL treatment was continued, and the PEGV dose was reduced by 50% up to 12 weeks. When IGF-I levels remained ≤1.2× ULN after 12 weeks, subjects were switched to PAS 60 mg monotherapy every 4 weeks. When IGF-I levels exceed 1.2× ULN after 12 weeks, patients were switched to PAS 60 mg and continued with 50% reduced PEGV dose. Between the 12 and 24 weeks period, PEGV dose alteration was not permitted unless IGF-I decreased below the age-adjusted normal limits. In these cases, the PEGV dose was reduced by 20 mg weekly until IGF-I levels reached their normal values (38). At baseline, the mean IGF-I was 0.97× ULN (95% CI, 0.91–1.02) with a mean PEGV dose of 134 mg/week (95% CI, 103–166). At 12 weeks, the mean IGF-I level increased to 1.59× ULN (95% CI, 1.45–1.73) and IGF-I ≤1.2× ULN was observed in 24.6% patients, so they were switched to the PAS monotherapy arm, by protocol. At 24 weeks, IGF-I levels were reduced into the reference

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Table 2 Novel medical therapies for acromegaly.

Drug	Mechanism of action	Clinical trial phase	Dosage	Biochemical efficacy (%)[a]	Effect on tumor mass	Main side effects
Pasireotide + Pegvisomant (38)	Somatostatin receptor ligand + GHR antagonist	Phase 4	Pasireotide 60 mg IM monthly + Pegvisomant 21-78 mg SC weekly	73.8	NA	Hyperglycemia, new-onset diabetes, gastrointestinal, myalgia, fatigue, headache, arthralgia, dizziness
Oral octreotide formulation (46)	Somatostatin receptor 2 ligand	Phase 3 completed (recently FDA approved)	20–40 mg 40 mg PO twice daily	58.2	NA	Gastrointestinal, blood glucose increase
Paltusotine ClinicalTrials.gov Identifier: NCT03789656 NCT03792555 NCT04261712	Somatostatin receptor 2 biased agonist	Phase 2 (active stage)	PO once daily (dosage not available)	NA	NA	NA
ATL1103 (51)	Antisense oligonucleotide inhibitor of GHR	Phase 2 completed	200 mg SC once or twice weekly	15	Not clinically significant	Injection-site reactions, elevated liver enzymes, headache, fatigue, gastrointestinal
ISIS 766720 ClinicalTrials.gov Identifier: NCT03548415	Antisense oligonucleotide inhibitor of GHR	Phase 2 (recruitment stage)	Single SC doses 28–28 days (dosage not available)	NA	NA	NA

[a]Attention to the different criteria of biochemical control between studies, specified in the text.
GHR, growth hormone receptor; IM, intramuscular; NA, not available; PO, per os (by mouth); SC, subcutaneous.

range in 93.3% of patients in the PAS monotherapy group and in 67.4% of patients in the combination group. Between baseline and 24 weeks, the mean PEGV dose could be decreased to 48 mg/week (95% CI, 21–74), whereas PEGV could be discontinued in 67.8% of patients (38). The most common adverse effect recorded was hyperglycemia (88.5%) with a frequency of diabetes mellitus (DM) increasing from 32.8% at baseline to 68.9% at 24 weeks. Baseline HbA1c was the main predictor of DM development at the end of the trial (38). This data indicated that PEGV was not able to compensate the hyperglycemia induced by PAS, probably due to the mechanism of action of the drugs: PEGV improves insulin sensitivity by antagonizing GH action, while the hyperglycemic effect of PAS is related to inhibition of insulin production by β-pancreatic cells, in addition to suppression of incretins, regardless of insulin resistance (38, 39).

This study demonstrated that PAS is a possible treatment option in patients previously controlled with the combination of fg-SRL and PEGV. This switch of SRL therapy has an important PEGV-sparring effect and a consequent reduction in the total cost of therapy. However, despite the high efficacy and supposed cost reduction, there is an increased risk of developing DM and health care costs related to this (38). Therefore, it is necessary to carefully choose the patients that would benefit the most from this new combination treatment, requiring further long-term studies.

In line with this, the PAPE extension study presented long-term 48 weeks results of efficacy and safety of PAS alone or in combination with PEGV treatment in acromegaly (40). It was a prospective, open-label, single-center follow-up study until 48 weeks after the core trial of 24 weeks, enrolling 59 out of 61 patients of the original study. At the end of the study, 77% of patients achieved normal IGF-I levels (≤1.2× ULN) with a mean IGF-I of 0.98× ULN (95% CI, 0.90–1.06). Stratifying for each treatment arm, 93.3% of subjects in the PAS monotherapy group had IGF-I normalization at 24 weeks, which was sustained at 48 weeks; while 67.4% of patients in the combination treatment group achieved IGF-I normalization at 24 weeks, which increased to 71.7% at 48 weeks (40). During extension, phase mean PEGV dose had to be increased from 47 to 64 mg/week (95% CI, 33–95), but with an overall cumulative PEGV dose reduction of 52% after 48 weeks compared to baseline, and 50.8% of patients were off PEGV treatment at the end of the trial, confirming PEGV-sparring effect of PAS (40).

Hyperglycemia remained the most common and important adverse event during the study, with an incidence of DM that increased from 68.9% at 24 weeks

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to 77% at 48 weeks. PAS-induced hyperglycemia was inversely correlated with baseline insulin secretion, indicating that the lower the insulin secretion at baseline, the greater will be the risk of hyperglycemia during treatment. No significant difference was observed in HbA1c levels between patients using PAS monotherapy and combination treatment at baseline (P = 0.36), 24 weeks (P = 0.72), and after 48 weeks (P = 0.26) (40). This extension study corroborates previously published data, which shows that PAS biochemically controls a large part of acromegaly patients with a 50% PEGV-sparring effect. However, it is associated with a high incidence of DM, which appears to be inversely related to the pancreatic β-cell ability to secrete insulin before starting treatment (40).

In addition, a recent study demonstrated the effectiveness of the synergistic action of the combination therapy PAS and PEGV in achieving biochemical control in six acromegaly patients resistant to all conventional medical treatments (41). The control group included 49 patients resistant to fg-SRL, but that were controlled with PAS (as monotherapy) or PEGV (as monotherapy or combined with fg-SRLs). The six patients in the study group were submitted to first-line treatment with pituitary neurosurgery, with except of only one patient due to technical difficulties with intubation and anesthesia induction. Because of tumor invasiveness characteristics and subtotal resection of the adenomas, all these patients received treatment with fg-SRL. Complete resistance was observed in all six patients and, consequently, this group was treated with second-line drugs, including combination therapy with fg-SRL and PEGV in two patients, PAS as monotherapy in three of them, and in one of the patients both treatments were tried. A second neurosurgery was performed on four of these six patients, seeking tumor debulking. After the failure of all other treatments, biochemical control of acromegaly was achieved in all 6 patients through combination therapy with PAS and PEGV. Regrowth of the residual tumor was not observed, and one patient presented a reduction of the lesion. A worsening of glycemic control occurred in one patient with previously DM, and new-onset impaired glucose tolerance was diagnosed in another, but these adverse effects were improved with the adjustment of previous insulin therapy and the introduction of a hypocaloric hypoglycidic diet, respectively. It is important to note that the study group was composed of tumors with a bad biochemical-radiological-histological prognosis, with higher GH levels, larger tumor dimensions and invasive nature, higher proliferative index (Ki-67) expression, and histopathological pattern of resistance to fg-SRL (low SST2 expression and low SST2/SST5 ratio). Albeit this study has a main limitation of the small sample size, it reinforces the important concept of personalized treatment in acromegaly, presenting a new possibility of combining medications for the control of aggressive disease (41).

New drugs from existing classes

Octreotide capsule

An oral formulation of octreotide capable of replacing the current medical treatment of acromegaly that requires lifelong use of parenteral drugs represents an interesting perspective on disease treatment for many patients. When administered orally, octreotide is mainly absorbed as an intact peptide in the jejunum, however the intestinal mucosa barrier, unfortunately, decreases its absorption, resulting in low plasma levels and low bioavailability (42).

The oral formulation of octreotide bypass this limitation with the introduction of transient permeability enhancer (TPE) technology, which can improve drug absorption through a transient and reversible opening of epithelial tight junctions in the small intestine, leading to high intestinal permeability (43). The tight junctions correspond to a transmembrane protein complex with an intestinal barrier function in relation to paracellular permeability of water-soluble macromolecules (43). Its function is dynamically regulated by a physiological extracellular stimuli, with an increase in permeability through, for example, bile salts and medium chain fatty acids (43). Octreotide capsule contains the TPE

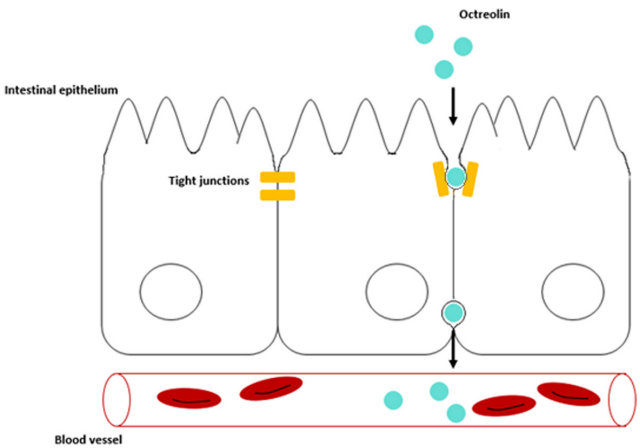

Figure 1
Mechanism of action of Octreolin. Octreotide capsules with transient permeability enhancer (TEP) technology, promotes a transient and reversible opening of epithelial tight junctions, crossing the intestinal barrier. This process improves the absorption of the drug and allows a serum therapeutic level of octreotide.

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technology which consists of a combination of medium chain fatty acid sodium salt with the drug peptide in an oily suspension in an enteric coating (Fig. 1) (43).

In preclinical studies, the pharmacokinetic profile in rats and primates demonstrated similar serum levels of octreotide after administration of oral capsules and SC injection, resulting in rapid and sustained suppression of GH levels in both administration models (43). This result demonstrates that the oral route retained the biological inhibitory activity of octreotide. Primate studies have shown safety without organ damage and a comparable toxicity profile between the octreotide capsule and injected dose (43). Intestinal permeability was demonstrated in rat models by fluorescent tracers showing that TPE transiently enhances permeability via paracellular transport by a rearranging of tight junctions proteins (ZO-1) in rats intestine (43). Intestinal permeability returned to baseline levels in 1–1.5 h after drug ingestion (43). Another important aspect demonstrated in the rat model was the inverse relationship between intestinal permeability and the molecule to be absorbed, with the best absorption presented with smallest dextrans molecules (4 kDa) coupled with TPE (43). Larger dextrans (40–70 kDa) were minimally absorbed, limiting the risk of internalization of intestinal pathogens and immunoglobulins (43). Limitation of time and size on intestinal permeability with TPE are two important aspects to favor safety in healthy individuals.

A phase 1 study was conducted in 75 healthy subjects using single doses (3, 10, 20 mg) of an octreotide capsule (Octreolin) and a single dose of 100 µg octreotide SC injection (44). Pharmacokinetics data showed that octreotide plasma concentration was dose-dependent following oral administration and a 20 mg dose was comparable to a 100 µg injection. After SC injection, octreotide reached peak levels in 0.6 h, while oral formulation increases more slowly with a serum peak in 2.7 h (44). Meanwhile, plasma octreotide concentration decreased with a comparable mean half-life for both routes of administration, reaching subtherapeutic levels (<0.5 µg/mL) after 6 h with injection and after 8 h with oral capsule (44). Food intake and proton pump inhibitors demonstrated a pronounced effect on Octreolin absorption, with almost 90 and 40% reduction in plasma concentration, respectively. In this study, an oral dosing of 20 mg strongly suppressed basal GH levels, reducing average GH concentration by 44% ($P < 0.05$). In addition, 80% of GH secretion induced by growth hormone-releasing hormone (GHRH)-arginine stimulation was significantly suppressed ($P < 0.001$) in the Octreolin-arm (44). Besides injection adverse effects, safety profile were comparable in both treatment groups, exhibiting an 8–15% incidence of gastrointestinal side effects and headache (44).

A phase 3 multicenter, open-label, dose-titration, case-controlled study was designed to test efficacy and safety of octreotide capsule in 155 acromegaly patients previously treated with stable doses of injectable SRLs for ≥3 months and that were complete or partially controlled (IGF-I < 1.3 ULN, and 2-h integrated GH < 2.5 ng/mL) (45). The main objective was to determine the efficacy of oral octreotide in maintaining biochemical control in patients who were prior responders to injectable SRLs. The first dose was administered 4 weeks after the last SRL injection, starting on 40 mg (20 mg twice daily, >1 h before or 2 h after a meal). In the titration phase, doses were progressively increased to values of up to 80 mg per day, according to IGF-I levels response, reaching a later maintenance phase with fixed doses for a core treatment of 7 months, followed by a voluntary 6 months extension. Of 102 subjects completing the core treatment, 86% elected to continue to the extension phase (45). Of the 151 evaluable individuals in the modified intention-to-treat group (all participants who had at least one efficacy assessment after first dose), 65% showed a sustained response and reached the primary endpoint of IGF-I < 1.3 ULN and mean integrated GH < 2.5 ng/mL at end of core treatment period, and 62% at end of extension period (13 months). Effect was durable and 85% of patients who entered the fixed-dose regime maintained their response for up to 13 months (45). Predictors of degree of oral capsule responsiveness included good baseline control on injectable SRLs (IGF-I ≤ 1 ULN, GH < 2.5 ng/mL) and low to mid doses of injectable SRLs (OCT-LAR < 30 mg or lanreotide autogel < 120 mg). Clinical control of acromegaly symptoms (headache, asthenia, perspiration, swelling of extremities and joint pain) also improved during the trial. At baseline, 81% of biochemically controlled subjects treated with SRL injections persisted with at least one active symptom of acromegaly. By the end of the fixed-dose phase, 54% of patients showed improvements and 26% maintained the severity of their symptoms (45). The most adverse effects were transient, resolved with treatment continuation, occurred at first 60 days of treatment and were not dose related. Of 155 patients, 89% experienced adverse effects of which 92% were classified as mild to moderate. Most common side effects were gastrointestinal (nausea, diarrhea, dyspepsia, abdominal pain, flatulence, vomiting), neurological (headache, dizziness), musculoskeletal (arthralgia, back pain).

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Twenty-three participants withdrew due to adverse events, 19 of them were study drug related. Two deaths were reported, but both were unrelated to the drug. Side effects were consistent with the already known SRL profile and acromegaly disease burden, with no safety signal related to the novel formulation and route of administration (45).

Oral octreotide was also evaluated in a 9-month phase 3 double-blind, randomized, placebo-controlled, multicenter study designed to evaluate efficacy and safety of octreotide capsule in acromegaly patients who demonstrated biochemical control on injectable SRL treatments (46). In this trial, 56 patients with acromegaly previously controlled (IGF-I ≤ 1.0 × ULN based on the average of two assessments) with injectable fg-SRL (on a stable dose for ≥3 months of therapy and using it for ≥6 months) were switched for oral octreotide or placebo. Normalization of IGF-I levels was maintained in 58% of patients treated with oral octreotide in comparison with 19% in the placebo group (P = 0.0079) (46). On June 26, 2020, FDA approved oral octreotide capsules as the first oral SRL for long-term maintenance treatment in patients with acromegaly who have responded to and tolerate treatment with injectable SRLs. This represents an improvement in the treatment arsenal of acromegaly, adding an effective and safe oral medication, an alternative for a significant proportion of patients from chronic injecting drug treatment.

Somatostatin receptor 2 biased agonist

Another emerging treatment is paltusotine (formerly known as CRN00808), an oral selective nonpeptide SST2 biased agonist. The term biased agonism reflects the ability of a ligand to selective activates a subset of a receptor's signaling pathway, different from other ligands (47, 48). In 2018, a phase 1, double-blind, randomized, placebo-controlled, single- and multiple-ascending dose trial was designed to evaluate safety, pharmacokinetics, pharmacodynamics and potential interaction with midalozam of this drug in 99 healthy volunteers (ClinicalTrial.gov Identifier: NCT03276858) (49). The data indicated that the drug was well absorbed with a half-life of 42–50 h, supporting once daily administration. The steady-state was reached in 3–5 days. Systemic exposure was markedly reduced when the capsule was taken with food, demonstrated as lower plasma CRN00808 area under curve (83%). Oral administration resulted in dose-dependent suppression of both GHRH stimulated GH and IGF-I secretion. Maximum GH-axis suppression was observed with 10 mg dose. Co-administration of midazolam in the drug interaction arm was performed to assess risk of interaction with CYP3A4/5 substrate, and results showed no midazolam pharmacokinetic changes with 20 mg of CRN00808, meaning little or no risk profile. Treatment adverse events were consistent with already known SRL profile and were generally mild and transient. Approximately 30% of subjects presented with gastrointestinal effects and mild elevations of pancreatic enzymes were reported in about 10% of participants. There was no serious event related to medication (49).

There are currently two active phase 2 clinical trials evaluating paltusotine in acromegaly. The ACROBAT EDGE is an open label exploratory study designed to evaluate the safety, efficacy, and pharmacokinetics of this drug in subjects with acromegaly that are treated with SRL regiments but do not respond completely to monotherapy (ClinicalTrials.gov Identifier: NCT03789656). The ACROBAT EVOLVE is a double-blind, placebo-controlled, randomized withdraw study to evaluate the safety, efficacy and pharmacokinetics of paltusotine compared to placebo in patients with acromegaly that respond to OCT-LAR or lanreotide depot monotherapy (ClinicalTrials.gov Identifier: NCT03792555). The EVOLVE and EDGE studies are conducted at the same centers globally and patients that complete either trial will be eligible to participate in an open-label extension study (ACROBAT ADVANCE). The ADVANCE is a phase 2, open label, long-term extension study designed to evaluate the safety and efficacy of paltusotine in acromegaly (ClinicalTrials.gov Identifier: NCT0461712).

New class of drugs

Antisense oligonucleotide

Antisense oligonucleotides are a single-stranded synthetic nucleotide sequence that binds to a specific mRNA, inhibiting the transcription of the gene and thus protein synthesis (50). ATL1103 is an antisense oligomer drug designed to block GHR expression, thereby lowering IGF-I levels (51). It has a chimeric arrangement consisting of a DNA core (or 'gap') of 20 nucleotides with a phosphorothioate backbone and flanked by 2′-O-methoxyethyl modifications of the terminal five nucleotides at each end, resulting in an increased plasma half-life and affinity for the mRNA (52). Thus, ATL1103 forms a complex with GHR mRNA and activates RNase H, which cleaves this hybrid, degrading GHR mRNA and preventing gene transcription (Fig. 2).

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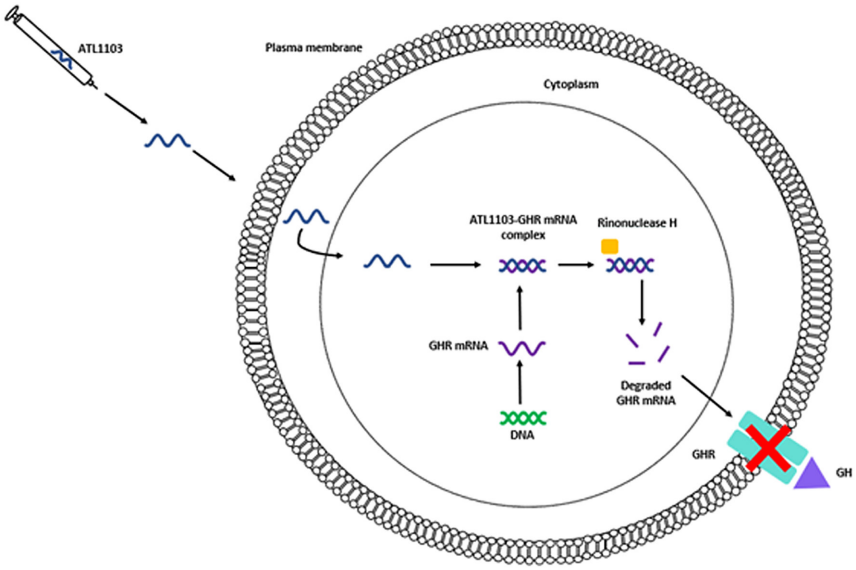

Figure 2
Mechanism of action of ATL1103. ATL1103, an antisense oligonucleotide drug, binds to growth hormone receptor (GHR) mRNA, activates ribonuclease H, which cleaves this complex, degrading the GHR mRNA. This process blocks gene transcription, inhibits the synthesis of GH-receptor (GHR) and, consequently, its binding to GH, ultimately decreasing insulin-like growth factor type I (IGF-I) levels.

In preclinical studies, ATL227446 (later renamed ATL1103) demonstrated promising results in modulating GH signaling (53). *In vitro* mouse cells, it knocked down GHR mRNA by 87%, and *in vivo* normal mice it resulted in 70% ($P < 0.0001$) reduction of GHR mRNA levels in liver tissue. This effect of inhibiting GH signaling was evidenced by a 59% decrease in serum IGF-I levels in mice treated for 10 weeks (53).

A phase 1 randomized, placebo-controlled, double-blind study tested subcutaneous (SC) doses of ATL1103 in 32 healthy male adults in two stages (54). In the single ascending dose stage of the trial, 24 subjects received four dose levels of ATL1103 or placebo, starting at 25 mg and escalating to 75, 250 and 400 mg. In the multiple dose stage, eight subjects received six doses of 250 mg of ATL1103 and four participants received placebo. The treated group showed a trend of reduction in IGF-I levels from days 14 to 28, with a statistically significantly effect ($P=0.034$) at day 21 with a 7% reduction in mean IGF-I levels vs baseline. Levels of GH-binding protein (GHBP), which is produced by cleavage from GH-receptor, were also statistically significant reduced by 16% ($P=0.007$) at day 21. Thus, this reduction provides support of the drug affinity for its target (54).

A phase 2 randomized, open-label, parallel-group study assessed the potential of ATL1103 as a treatment for acromegaly (51). Twenty-six patients with active acromegaly (IGF-I levels > 1.3 ULN at screening visit) were equally divided into two study arms, receiving 200 mg ATL1103 once or twice weekly for 13 weeks. After completion of the drug administration period, patients were monitored for an additional 8 weeks, without acromegaly therapy. At week 14, the twice-weekly regiment resulted in a medial fall in IGF-I levels of 27.8% ($P=0.0002$) compared to baseline, with 2 (15%) of 13 patients achieving an IGF-I level within the reference range. No change in IGF-I occurred with once-weekly dosing. In the twice-weekly cohort, IGF-I levels were still declining at week 14 and remained lower by a median of 18.7% ($P=0.0005$) at the end of the washout period (week 21). This suggests that the duration of ATL1103 study therapy was too short to achieve maximum effectiveness and prolonging treatment at the doses used could result in a greater decline in IGF-I levels. GHBP levels also showed a significant decline at week 14, with a median decrease of 23.6 and 48.8% in the once and twice-weekly cohorts ($P=0.027$ and $P=0.005$), respectively. These results were maintained until week 21. GH levels had increased by a median of 46% at week 14 ($P=0.001$) in the twice-weekly regiment, but no change was demonstrated in the once weekly group. ATL1103 was well tolerated, although 85% of patients in both cohorts experienced mild-to-moderate injection site reactions. Four serious adverse effects were reported, but none were felt to be drug related. There were no significant changes in pituitary tumor size, but the short duration of the study is a limitation to evaluate this effect (51).

Therefore, the current findings of ATL1103 demonstrate a proof of concept that GH-receptor antisense oligomer lowers IGF-I levels in acromegaly. It has the potential to achieve disease control, but more studies with higher doses and/or longer duration treatment are needed to determine the potential of this novel therapy.

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Currently, there are two clinical trials involving another antisense inhibitor of the GHR, both at the recruitment stage. The first one is a double-blind, placebo-controlled phase 2 study, designed to assess the safety, tolerability, and efficacy of ISIS 766720 (IONIS-GHR-LRx) administered once every 28 days for 16 weeks in 60 patients with acromegaly being treated with fg-SRLs. These patients must be on stable maximum or maximally tolerated dose of fg-SRL with a serum IGF-I between 1.3 and 5× ULN, adjusted for age and sex, at screening (ClinicalTrials.gov Identifier: NCT03548415). The other clinical trial is an open-label extension trial of the same drug, including all the 60 participants that will remain on the same dose from previous study for 53 weeks. At the end of this period, participants will enter a 14-week post-treatment evaluation course (ClinicalTrials.gov Identifier: NCT03967249).

Precision medicine in the treatment of acromegaly

Considering all the available options for acromegaly treatment and all the emerging drugs under evaluation, the current treatment scenario, where the majority of patients receive the same treatment (fg-SRL) after surgical failure, can be optimized by the description of biomarkers of response, that help to identify the best drug for each individual patient. Some biomarkers have been described in the literature and several groups are working in the description of biomarkers that will allow a more individualized treatment.

For fg-SRL the most robust predictor of response is SST2 expression, with a lower chance of disease control in patients with low expression of this biomarker. In addition, other biomarkers have been described, like tumor intensity on T2-weighted sequence of MRI, pre-treatment IGF-I levels, age and body weight (55, 56). Other molecular or pathological biomarkers have also been proposed, although they still lack standardization and reference values for clinical application (57, 58, 59, 60, 61, 62, 63).

Expression of SST2 has been suggested to be a predictor of pasireotide response, but SST5 seems to be a better predictor in patients resistant to fg-SRL treatment (60, 64, 65). However, those patients with low SST2 expression may have a better tumor shrinkage with pasireotide (66). For pegvisomant, some predictors have been described like pre-treatment GH and IGF-I levels, age and BMI (67). Expression of exon3-deleted growth receptor has been proposed as a predictor of response to pegvisomant in some studies, although it has not been confirmed in larger series (68, 69).

Although biomarkers have been described for different treatments of acromegaly, there is still a need for improvement in this field, especially with larger studies applying robust methodology that will allow standardization in the analysis of these biomarkers, and application in the clinical practice.

Conclusion

Acromegaly is a life-threatening disease with a great burden on the individual's quality of life when biochemical control is not achieved. Current medical therapy, while effective and relatively safe, does not achieve disease control in a proportion of patients. Therefore, novel formulations or combinations of current approved drugs and new molecules in clinical development will bring a new horizon for these cases. Advances in scientific knowledge of the characteristics of pituitary tumors (growth pattern, gene mutations, immunohistochemical aspects) and patients particular aspects (comorbidities, GH/IGF-I levels) will help to determine biomarkers of disease response allowing an individualized treatment rather than a universal algorithm approach.

Declaration of interest

M R G has received unrestricted research grants and lecture fees from Novartis, Ipsen and Pfizer; has participated on advisory boards for Novartis and Ionis; and is a PI in clinical trials by Novartis and Crinetics. L K has received lecture fees from Novartis, Pfizer and Ipsen and has participated as a co-investigator in clinical trials by Novartis and Ipsen. B M has nothing to disclose.

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9- Anexo III: Capítulo de livro publicado

Hiperprolactinemia

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Introdução

A prolactina (PRL) é um hormônio hipofisário responsável pelo processo de lactação, cuja síntese e secreção ocorrem principalmente nas células lactotróficas da hipófise anterior, mas também no sistema nervoso central, sistema imune, útero, placenta e glândulas mamárias.[1] Os principais estímulos fisiológicos à sua síntese e secreção são amamentação, esteroides ovarianos (principalmente estrogênio) e estresse. A regulação de sua secreção é complexa e envolve neurotransmissores, neuro-hormônios, substratos metabólicos e neuropeptídeos. Alguns neuro-hormônios hipotalâmicos, como hormônio liberador de tireotrofina (TRH), ocitocina e o hormônio polipeptídico peptídeo intestinal vasoativo (VIP), estimulam a secreção de PRL. No entanto, a principal influência do hipotálamo sobre a secreção de PRL é por meio da dopamina, a qual atua nos receptores dopaminérgicos tipo 2 (D2) presentes nos lactotrofos, reduzindo a síntese e secreção de PRL.[2]

A hiperprolactinemia, definida pelo aumento dos níveis séricos de PRL acima do limite superior da normalidade, é uma situação bastante comum na prática clínica. Suas causas podem ser divididas em fisiológicas, farmacológicas e patológicas, sendo os prolactinomas a causa mais frequente de hiperprolactinemia patológica.[3]

Os prolactinomas representam cerca de 53% (41%-66%) de todos os tumores hipofisários e ocorrem mais comumente em mulheres entre a 2ª e a 5ª década de vida, em uma proporção de sexo de 10:1.[4,5] Durante esse período predominam os tumores < 1 cm (microadenomas), enquanto em homens e mulheres na pós-menopausa há um predomínio de tumores ≥ 1 cm (macroadenomas).[3] Após a 5ª década de vida, a prevalência é similar em ambos os sexos.

Etiologias

Podemos dividir as causas de hiperprolactinemia em três grandes grupos: fisiológicas, farmacológicas e patológicas **(Quadro 1)**.

Quadro 1. Causas de hiperprolactinemia

Causas fisiológicas	Gravidez Amamentação Estresse Atividade física Sono Estimulação mamária
Causas farmacológicas	Estrogênio, antidepressivos tricíclicos e IRS Antipsicóticos Anti-hipertensivos Procinéticos Narcóticos (cocaína, opiáceos)
Causas patológicas	Doenças sistêmicas: hipotireoidismo primário, doença renal crônica, cirrose hepática, insuficiência adrenal Neurogênicas: tesões da parede torácica, medula espinhal Crises convulsivas Doenças hipotalâmico-hipofisárias: prolactinomas, acromegalia, doença de Cushing, sela vazia, hipofisite linfocítica, craniofaringioma, meningioma, disgerminoma, glioma, sarcoidose, histiocitose, tuberculose, irradiação

Elaborado pelos autores.

Causas fisiológicas

A avaliação inicial de uma hiperprolactinemia deve levar em consideração causas fisiológicas, como gravidez, amamentação, estresse, atividade física, sono e estimulação mamária. Durante a gravidez ocorre uma hiperplasia lactotrófica devido aos altos níveis de estrógeno, levando consequentemente à hiperprolactinemia. O processo de lactação leva a um aumento importante dos níveis de PRL, que tendem a normalizar aproximadamente 6 meses após a interrupção da amamentação.[6,7]

Causas farmacológicas

A causa mais comum de hiperprolactinemia não patológica é o uso de fármacos que elevam os níveis séricos de PRL, o que ocorre por meio de diferentes mecanismos.[8] As drogas mais envolvidas são os antipsicóticos e antidepressivos, e os mecanismos envolvem um aumento na transmissão de serotonina e redução na de dopamina. Em casos de hiperprolactinemia secundária ao uso de medicações, deve-se suspender, quando possível, a medicação por pelo menos 72 horas e repetir a dosagem de PRL.[8] Caso não haja possibilidade de suspensão dos medicamentos, solicita-se a ressonância magnética (RM). Na hiperprolactinemia farmacológica, os níveis de PRL não costumam exceder 100 μg/L.[1]

Fármacos antidepressivos (tricíclicos e inibidores da recaptação de serotonina – IRS), anti-hipertensivos (como verapamil e metildopa), narcóticos (morfina e cocaína) e fármacos contendo estrógenos (como anticoncepcionais) levam, em geral, à hiperprolactinemia leve e raramente sintomática.[6,7]

Drogas antipsicóticas são as mais envolvidas na hiperprolactinemia e, com o uso crônico, cerca de 40%-90% dos pacientes mantêm níveis elevados de PRL. A hiperprolactinemia nesses casos ocorre por meio do antagonismo dos receptores D2 na hipófise anterior, em especial com uso de haloperidol e risperidona, que têm uma alta afinidade por esses receptores. Por outro lado, os antipsicóticos atípicos quetiapina e aripiprazol podem reduzir os níveis de PRL.[9]

Alguns agentes procinéticos, como metoclopramida e domperidona, também antagonizam os receptores D2 e podem levar à hiperprolactinemia, que ocorre em cerca de 50% dos pacientes em uso dessas medicações.[7]

O abuso de opioides pode causar hiperprolactinemia por meio da mediação de receptores opiáceos no hipotálamo; o uso de cocaína, maconha e álcool também pode elevar os níveis de PRL.[2,10]

O agente anti-hipertensivo verapamil, que pertence à classe de bloqueadores de canal de cálcio não diidropiridínicos, pode levar à hiperprolactinemia pela supressão de dopamina tuberoinfundibular; isso não ocorre com outras drogas da mesma classe, como diltiazem e nifedipino. A metildopa, outro fármaco anti-hipertensivo, também pode levar à hiperprolactinemia pela inibição da síntese de dopamina.[2]

Causas patológicas

A hiperprolactinemia também pode ser secundária a algumas doenças sistêmicas. O hipotireoidismo primário cursa com hiperprolactinemia em cerca de 8%-43% dos casos e se deve ao estímulo do TRH em síntese de PRL, bem como à ausência do efeito direto da tiroxina nos receptores dopaminérgicos em nível hipofisário e hipotalâmico. A hiperprolactinemia pode ser detectada em até 22% de pacientes com hipotireoidismo subclínico.[10,11] Na hiperprolactinemia induzida por hipotireoidismo, pode ocorrer hipertrofia hipofisária, a qual pode ser confundida com prolactinoma (pseudoprolactinoma). O tratamento do hipotireoidismo leva à normalização dos níveis de PRL e à redução do volume da hipófise.

A disfunção renal crônica pode levar à hiperprolactinemia devido à depuração renal reduzida de PRL e a um aumento de sua secreção. Nas hepatopatias, há aumento dos níveis séricos de estrógenos e menor inibição da PRL, podendo ocasionar aumento dos seus níveis séricos.[2,11]

Pacientes com insuficiência adrenal podem cursar com hiperprolactinemia, uma vez que os glicocorticoides têm um efeito supressor na síntese e secreção de PRL.[10]

A hiperprolactinemia neurogênica ocorre por meio da ativação de vias aferentes medulares, secundária a lesões da parede torácica (p. ex., em casos de herpes-zóster, queimaduras e cirurgias torácicas) ou da medula espinhal.[10]

A hiperprolactinemia pode ocorrer após crises convulsivas, especialmente tônico-clônicas generalizadas, devido a uma propagação da atividade epiléptica ao eixo hipotálamo-hipófise.[2]

Tumores hipotalâmico-hipofisários podem causar hiperprolactinemia devido à compressão da haste hipofisária (efeito haste será detalhado posteriormente). Doenças infiltrativas, síndrome da sela vazia e secção de haste hipofisária também podem cursar com hiperprolactinemia por efeito haste, cujos níveis raramente excedem 100 μg/L.[10]

Os prolactinomas são a principal causa de hiperprolactinemia patológica e, em uma metanálise brasileira, foram responsáveis por cerca de 51% dos casos de hiperprolactinemia em 1.234 pacientes.[12]

Apresentação clínica

Em mulheres, os sinais e sintomas de hiperprolactinemia incluem galactorreia, distúrbios menstruais e infertilidade. Se não houver tratamento, o hipogonadismo prolongado pode resultar em redução de massa óssea e aumento do risco de fraturas. Em mulheres na pré-menopausa, os sintomas mais comuns são amenorreia e infertilidade; galactorreia ocorre em cerca de 80% dos casos. Dispareunia e baixa libido também podem ocorrer devido à deficiência estrogênica.[13]

Em homens, a hiperprolactinemia pode se manifestar por hipogonadismo, redução de libido, disfunção erétil, ginecomastia, infertilidade e, mais raramente, galactorreia. Pacientes com hipogonadismo prolongado e sem tratamento também podem apresentar redução de massa óssea.

Cerca de metade dos homens com prolactinomas apresenta sintomas locais, secundários a efeitos de massa tumoral, uma vez que a prevalência de macroprolactinomas é maior nos homens quando comparados às mulheres.[11,14]

Macroprolactinomas podem exercer efeitos de massa e gerar sintomas compressivos, como déficit visual, que ocorre por compressão quiasmática, cefaleia e deficiência de hormônios hipofisários (hipopituitarismo), desencadeado por compressão direta do tecido hipofisário ou da haste. A alteração visual tipicamente relacionada à compressão de quiasma óptico é a hemianopsia bilateral, mas diversas alterações podem ser encontradas, inclusive amaurose. Macroprolactinomas raramente podem evoluir com hidrocefalia e hipertensão intracraniana.

Apesar de incomuns em crianças, os prolactinomas nessa faixa etária normalmente se manifestam com sintomas locais e atraso puberal.[11]

Mais raramente, apoplexia hipofisária pode ser a manifestação clínica inicial de um prolactinoma, caracterizada por sintomas como cefaleia súbita e intensa e perda visual aguda.[14,15]

Nos últimos anos, a hiperprolactinemia tem sido associada a alterações metabólicas e ganho de peso, como consequência de efeitos orexígenos gerados pela regulação hipotalâmica.[16] No entanto, essa associação ainda é controversa e estudos são necessários para comprová-la, assim como os efeitos do tratamento sobre essas alterações metabólicas.

Diagnóstico

Laboratorial

A dosagem da PRL sérica deve ser feita apenas diante de uma suspeita clínica de hiperprolactinemia, e não como exame de rotina. Hiperprolactinemia deve ser sempre confirmada com uma segunda dosagem, atentando-se às causas fisiológicas e farmacológicas.[14]

A PRL circulante tem tamanhos variáveis, e, em indivíduos saudáveis, predomina a forma monomérica (peso molecular 23 KDa). As formas diméricas (ou *big prolactin*), cujo peso molecular é de 45-60 KDa, e a macroprolactina (ou *big-big prolactin*), com peso molecular de 150-170 KDa, correspondem a menos de 20% das isoformas de PRL.[17] A PRL dimérica e a macroprolactina têm mínima atividade biológica, porém ambas podem interferir na dosagem de PRL. A frequência de macroprolactinemia em pacientes com hiperprolactinemia varia de 15% a 46%.[18]

A presença de macroprolactinemia pode ser investigada por meio do ensaio de precipitação em polietilenoglicol (PEG). A macroprolactina precipita juntamente com o PEG, deixando apenas as formas monoméricas no sobrenadante. Uma recuperação maior do que 60%, ou seja, se a PRL após precipitação corresponder a 60% ou mais da forma *in natura*, indica a presença da forma monomérica. Se essa recuperação for menor do que 40%, temos a macroprolactinemia. Em pacientes assintomáticos nos quais foi detectado aumento de PRL, recomenda-se realizar a dosagem de macroprolactina.[19]

Outra armadilha na avaliação da hiperprolactinemia é o efeito gancho, que ocorre quando são utilizados imunoensaios com dois sítios diferentes (imunorradiométricos ou

quimioluminescência) e níveis muito elevados de PRL saturam os dois anticorpos, impedindo a formação dos "complexos sanduíches" e levando a resultados falsamente muito mais baixos (normais ou levemente aumentados).[14,20] Em pacientes com macroadenomas grandes (≥ 3 cm) cujos níveis de PRL estão pouco aumentados ou até mesmo normais, deve-se realizar a diluição da amostra 1:100.[7,8]

Lesões selares, principalmente os adenomas clinicamente não funcionantes (ACNF), e parasselares podem levar à compressão da haste hipofisária e à interrupção do influxo dopaminérgico à hipófise anterior, gerando uma hiperprolactinemia leve, em geral de < 100 µg/L (efeito haste).[21] Em geral, os níveis de PRL correlacionam-se com o tamanho do prolactinoma: a grande maioria dos pacientes com microprolactinomas apresenta níveis séricos de PRL de até 100 µg/L, e praticamente todos os pacientes com macroprolactinomas terão níveis de PRL acima de 100 µg/L. Os níveis de PRL costumam exceder 250 µg/L em pacientes com macroprolactinomas grandes. Níveis de PRL acima de 250 µg/L são encontrados quase exclusivamente em macroprolactinomas, sendo utilizados como *cut-off* para diferenciá-los de ACNF.[22] Prolactinomas císticos têm uma menor quantidade de células lactotróficas, podendo haver menores níveis de PRL.[10]

Por imagem

Uma vez diagnosticado um quadro de hiperprolactinemia patológica, ou seja, afastadas causas fisiológicas e medicamentosas, o próximo passo é a realização do exame de imagem, preferencialmente a RM de sela túrcica.[23] Nas imagens ponderadas em T1, os prolactinomas se apresentam com aspecto hipointenso (mais comum) ou isointenso. Raramente podem ser encontradas lesões com sinal, hiperintensas, indicando transformação hemorrágica do tumor.[14] Já as imagens ponderadas em T2 têm aspecto mais heterogêneo, porém, em sua maioria, são hiperintensas **(Figuras 1 e 2)**.[14]

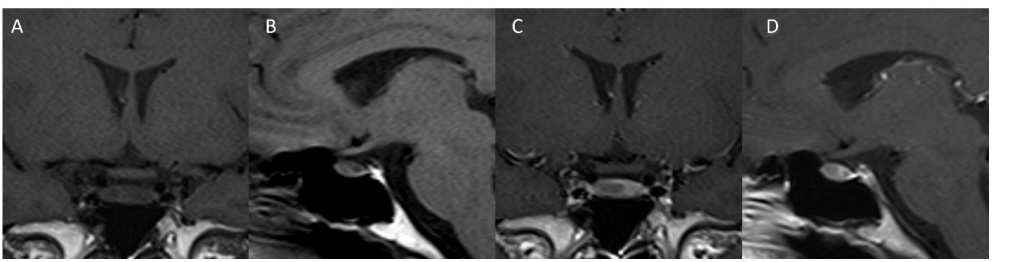

Figura 1. Ressonância magnética de sela túrcica evidenciando microprolactina à direita da adeno-hipófise. Lesão levemente isointensa nas sequências ponderadas em T1 (A corte coronal e B corte sagital) e com realce discreto pelo contraste em relação à hipófise normal (C corte coronal e D corte sagital com contraste)
Arquivo pessoal dos autores.

A tomografia computadorizada de hipófise tem pouca função na avaliação diagnóstica dos prolactinomas, mas pode ser útil para a verificação de suspeita de erosão óssea esfenoidal, como em casos de macroprolactinomas invasivos.[14]

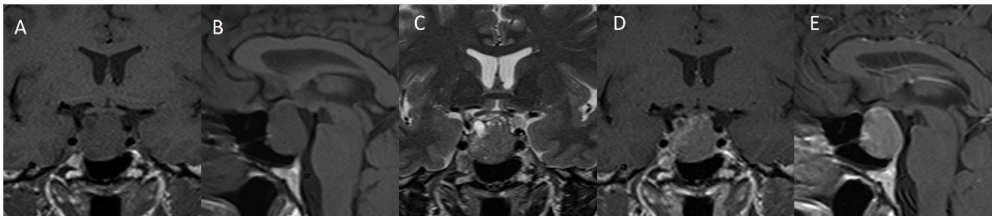

Figura 2. Ressonância magnética de sela túrcica mostrando macroprolactinoma. A: lesão isointensa no corte coronal sem contraste, ocupando toda a região selar, com expansão infrasselar e suprasselar, comprimindo quiasma óptico. B: corte sagital. C: corte coronal em T2, mostrando lesão isointensa com áreas hipertensas, sugerindo degeneração cística. D e E: cortes coronal e sagital pós-contraste, mostrando lesão com pouco realce pelo contraste.
Arquivo pessoal dos autores.

Tratamento

Os objetivos do tratamento de um prolactinoma consistem em controlar a secreção hormonal excessiva e suas consequências, particularmente as relacionadas ao hipogonadismo, além de controlar efeitos de massa tumoral, evitando distúrbios compressivos locais. Contudo, nem todo paciente com prolactinoma tem indicação de tratamento. Estudos sobre a história natural dos microprolactinomas não tratados revelam que o crescimento persistente ou significativo desses tumores é raro.[14] Portanto, pacientes assintomáticos com microprolactinomas não necessitam de tratamento, podendo ter apenas acompanhamento clínico e laboratorial.[24]

Além disso, mulheres na pré-menopausa em amenorreia e sem desejo de gestar podem receber terapia hormonal combinada (estrogênio + progesterona) caso não desejem tratamento ativo do microprolactinoma.[25] Já nos casos de macroprolactinomas, o tratamento é aconselhável, pois, em geral, são tumores com propensão ao crescimento e sintomáticos.[26]

As atuais opções de tratamento para os prolactinomas incluem: medicamentoso, cirúrgico e radioterápico.

Medicamentoso

Os agonistas dopaminérgicos (DA) representam o tratamento de primeira linha para a maior parte dos casos de pacientes com prolactinoma.[24] Atualmente, há a disponibilidade de dois fármacos nessa classe de medicação: bromocriptina e cabergolina. Os DA têm efeito bem documentado na diminuição dos níveis de PRL e do volume tumoral, independentemente do sexo e do tamanho do adenoma.[14,23]

A bromocriptina foi o primeiro fármaco DA a ser utilizado na prática clínica, sendo introduzido na Europa no início da década de 1970.[27] É um derivado da ergotamina com propriedades agonistas não seletivas para os receptores de dopamina (D1R e D2R). A dose inicial é de 1,25 mg/dia e é gradualmente aumentada para 2,5 mg por 2 vezes/dia a cada 7-10 dias, de acordo com a tolerância do paciente e os níveis de PRL, que devem ser acompanhados a cada 1 a 2 meses.[28] A maioria dos pacientes obtém resposta terapêutica com 7,5 mg/dia, não necessitando de doses maiores.[28]

A cabergolina é também um derivado da ergotamina e corresponde ao DA mais amplamente utilizado e recomendado pelas sociedades de Endocrinologia.[17] Tem a vantagem de maior seletividade ao D2R e maior meia-vida, podendo ser administrada 1 a 2 vezes/semana na maioria dos casos.[28] Recomenda-se iniciar o tratamento com doses de 0,25-0,5 mg/semana,

com aumento gradual a cada 2 a 3 meses, de acordo com a resposta dos níveis de PRL e da redução tumoral.[6,17,23] Em geral, o controle da doença é alcançado com doses de 0,5-3,0 mg/semana, sendo que casos de macroprolactinomas podem necessitar de doses maiores e um escalonamento mais rápido.[14,23]

Efeitos adversos

Em geral, os DA apresentam efeitos adversos mínimos, sendo medicamentos bem tolerados. Os mais comuns são: náusea, vômitos, cefaleia, tontura, hipotensão postural, fadiga, congestão nasal, constipação e dor abdominal.[6,23] Esses efeitos adversos podem ocorrer logo após o início da medicação e quando há o aumento de sua dosagem, sendo minimizados por meio da introdução do DA em uma dosagem inicial baixa, juntamente com uma pequena refeição ao deitar, associado a uma adequada de ingesta hídrica e recebendo posterior incremento de dose, quando necessário, de forma gradual.[6,23] Efeitos mais raros são: fenômeno de Raynaud; pericardite constritiva; fibrose pleuropulmonar. Além disso, o tratamento medicamentoso de macroprolactinomas invasivos pode resultar em casos de rinorreia liquórica e herniação do quiasma óptico quando ocorre uma rápida redução do volume tumoral, removendo parcialmente a região do adenoma que recobria o defeito da base do crânio.[14] Dois potenciais efeitos adversos graves que sempre devem ser investigados correspondem às valvulopatias cardíacas e aos transtornos psiquiátricos.[14,17,24]

A associação entre doença cardíaca valvar e o uso prolongado de DA foi demonstrada em estudos envolvendo pacientes com doença de Parkinson e seu tratamento com altas doses de DA (cabergolina > 3 mg/dia), não sendo utilizadas no tratamento de prolactinoma.[29,30] Esse risco está principalmente relacionado às propriedades agonistas dos DA em relação aos receptores serotoninérgicos 5-HT2B presentes nas valvas cardíacas.[29,30] O risco foi significativamente maior com o uso da cabergolina e da pergolida do que com os demais DA.[29,30] Desde 2007, inúmeros estudos foram realizados com o objetivo de demonstrar a associação entre as alterações valvares cardíacas e o tratamento com DA (principalmente a cabergolina) na hiperprolactinemia, e, embora essa questão ainda não esteja totalmente esclarecida, o risco parece ser muito baixo.[14] Em 2019, com base nesses dados, uma força multitarefa envolvendo a British Society of Echocardiography, British Heart Valve Society e Society of Endocrinology publicou como recomendação a realização de um ecocardiograma transtorácico antes do início do tratamento com DA para hiperprolactinemia e em intervalos de 5 anos, caso a dosagem da cabergolina seja ≤ 2 mg/sem. Aqueles pacientes que necessitam de tratamento com doses > 2 mg/sem precisam fazer ecocardiograma transtorácico anual.[31]

Outro importante efeito adverso dos DA, muitas vezes negligenciado na consulta, corresponde aos distúrbios psiquiátricos, que podem se apresentar como mania, psicose, depressão, ansiedade, confusão mental, alucinações auditivas, insônia, paranoia e transtornos do controle do impulso.[32] Esses distúrbios podem se manifestar como novos sintomas, logo após o início da medicação, ou se exacerbar em pacientes com doenças psiquiátricas prévias.[32] Dentre os distúrbios psiquiátricos, os transtornos do controle do impulso são os mais comuns, podendo se apresentar como: jogar patológico, comprar compulsivo, comer compulsivo e hipersexualidade.[14,32] Embora os DA exerçam sua função terapêutica nos prolactinomas ao se ligarem aos D2R, também têm (baixa) afinidade aos D3R, altamente expressos no sistema mesolímbico.[32] É por meio dessa ligação excessiva que ocorrem os efeitos adversos neuropsiquiátricos.[32] Eles podem ser altamente danosos para o paciente e seu meio social, mas são reversíveis após a suspensão dos DA.[32] Fatores de risco para o desenvolvimento de transtornos

de comportamentos compulsivos são: dosagem dos DA, sexo masculino, idade jovem e ser solteiro.[32] Devido à sua potencial gravidade e reversibilidade com a retirada da medicação, é necessária uma investigação ativa de sinais e sintomas sugestivos desses transtornos.

Acompanhamento e retirada dos agonistas dopaminérgicos

Os DA devem ser iniciados com doses baixas, minimizando o risco de efeitos adversos, e receber incrementos progressivos a cada 2 a 3 meses, objetivando níveis normais de PRL.[23] Pacientes com microprolactinomas e com níveis de PRL normalizados com o tratamento podem ter sua reavaliação hormonal realizada anualmente.[23] Em casos de macroprolactinomas, é recomendada a realização de RM da hipófise em 2 a 3 meses após o início da medicação, com intervalos posteriores mais espaçados, além de avaliação laboratorial (PRL) a cada 3 meses.[23] Casos com macroadenomas hipofisários com extensão suprasselar e próximos ao quiasma óptico (< 2 mm de distância) devem ter seu campo visual avaliado com a campimetria manual (Goldmann).

A retirada dos DA pode ser tentada sob condições ideais, a fim de minimizar o risco de recorrência da hiperprolactinemia. Recomenda-se a descontinuação da medicação após 2 anos de tratamento naqueles pacientes que apresentam níveis normais de PRL após o desmame gradual do fármaco e com RM revelando o desaparecimento do tumor ou redução de seu volume em mais de 50%.[23,24] Os pacientes de melhor prognóstico à retirada da medicação são aqueles com menores níveis de PRL ao diagnóstico, maior queda da PRL nos primeiros meses de tratamento com DA e com tumores menores e menos invasivos.[33]

Em geral, as recorrências ocorrem no primeiro ano após a retirada da medicação, sendo, portanto, recomendada a monitorização dos níveis de PRL a cada 3 meses no primeiro ano e, após tal período, anualmente.[24] Além disso, preconiza-se solicitar uma RM caso haja aumento dos níveis de PRL acima dos valores de referência.[24] Naqueles pacientes que apresentam hiperprolactinemia recorrente, uma segunda retirada do DA pode ser benéfica após 2 anos adicionais de tratamento, mas com chances de eficácia similares às da primeira tentativa.[34]

Resistência aos agonistas dopaminérgicos

A definição de resistência aos DA ainda não é uniforme até o momento, o que influencia diretamente a avaliação das taxas de eficácia do tratamento medicamento e os preditores de resposta. Contudo, a maior parte das diretrizes sugere considerar falha de tratamento clínico quando os níveis de PRL não são normalizados e/ou quando há falha em reduzir em > 50% o volume tumoral, utilizando doses padronizadas das medicações (bromocriptina 7,5 mg/dia ou cabergolina 2 mg/sem) por um período mínimo de 6 meses.[17,24,35]

Os mecanismos patológicos responsáveis pela resistência aos DA ainda não estão totalmente elucidados, mas incluem redução na expressão e, consequentemente, na densidade de D2R nos lactotrofos resistentes; variação na proporção de isoformas curtas e longas dos D2R; alteração na cascata de sinalização do D2R (p. ex., diminuição da proteína G, responsável pela ligação do D2R à adenilato ciclase, diminuindo a capacidade do DA em inibir a secreção de PRL).[17,24] A resistência aos DA ocorre em aproximadamente 20% a 30% dos pacientes tratados com bromocriptina e em 10% a 15% daqueles tratados com cabergolina.[17,36]

As alternativas terapêuticas possíveis nesses casos são: trocar o DA utilizado (em geral, bromocriptina para cabergolina, não o reverso); aumentar a dose de DA caso o paciente continue a apresentar resposta e tolerar a medicação; cirurgia; radioterapia; e tratamentos experimentais.[17,24]

Escalonamento da dose

O aumento da dose do DA pode ser benéfico para os pacientes com resistência parcial à medicação. Enquanto houver uma resposta contínua e progressiva e ausência de efeitos colaterais, pode-se realizar o escalonamento gradual da cabergolina (droga mais efetiva).[17,24] Contudo, deve-se atentar para o risco de valvulopatia cardíaca com altas doses de cabergolina.[29,30]

Cirurgia

As diretrizes atuais recomendam o tratamento cirúrgico como terapia adjuvante, principalmente nos casos de pacientes com resistência ou intolerância aos DA.[23,24] Outras indicações cirúrgicas clássicas incluem casos de complicações tumorais agudas, como apoplexia hipofisária sintomática e rinorreia liquórica, além da expansão tumoral sintomática e refratária ao tratamento medicamentoso durante a gestação.[14] A neurocirurgia também deve ser considerada para aquelas mulheres com macroprolactinomas e com desejo de gestar e em casos de pacientes com contraindicações ao tratamento com DA, como transtornos do controle do impulso.[14]

Recentemente, têm-se considerado outras indicações, tais como pacientes jovens com altas chances de ressecção tumoral completa (microprolactinomas ou macroprolactinomas não invasivos) e que não desejam tratamento medicamentoso em longo prazo; pacientes com prolactinomas císticos, embora os DA também tenham eficácia comprovada nesses casos, apresentando normalização dos níveis de PRL (em 82% dos casos), redução tumoral (em 70% dos casos) e descompressão de quiasma óptico.[14,23,37] Além disso, deve-se avaliar a realização de cirurgia de redução tumoral (*debulking*) naqueles indivíduos com doses de DA acima do padrão recomendado, uma vez que, mesmo que a ressecção seja incompleta, há benefício no controle bioquímico tumoral e redução da dose medicamentosa.[14,17]

A cirurgia transesfenoidal representa o tratamento padrão-ouro para as cirurgias hipofisárias, reservando a cirurgia transcraniana para casos mais raros, envolvendo prolactinomas gigantes, com importante extensão suprasselar.[14,17] Revisões de casos cirúrgicos demonstram uma taxa de remissão média inicial caracterizada por normalização dos níveis de PRL entre 1 e 12 semanas de pós-operatório, de 74,7% em pacientes com microprolactinoma e de 33,9% naqueles com macroprolactinomas.[38] A taxa de sucesso cirúrgico ao longo das séries não é uniforme, variando de 38% a 100% nos microprolactinomas e 6,7% a 80% nos macroprolactinomas.[38] As taxas de recorrência, por sua vez, apresentam valores médios de 18,2% para microprolactinomas e 22,8% para macroprolactinomas.[38] Os fatores preditores de remissão em longo prazo encontrados foram os níveis iniciais (pré-operatórios) de PRL (< 200 μg/L) e o grau de invasão tumoral ao seio cavernoso.[14,38]

A cirurgia transesfenoidal representa um procedimento seguro e com baixos índices de complicação quando realizada em centros de referências e por neurocirurgiões experientes. Sua taxa de mortalidade geral é muito baixa (< 0,5%), assim como as taxas de complicações maiores (perda visual, rinorreia liquórica, meningite/abscesso, infarto cerebral e hemorragia intracraniana), que ocorrem em 1% a 3% dos pacientes.[14] Outras complicações possíveis são o hipopituitarismo, o diabetes *insipidus* (transitório ou permanente) e a síndrome da secreção inapropriada de hormônio antidiurético. Assim como ocorre com os demais adenomas hipofisários, o risco de complicações e morbidade pós-operatória é inversamente proporcional ao tamanho do prolactinoma.[14,38]

A utilização de tratamento medicamentoso com DA como terapia pré-operatória à cirurgia transesfenoidal ainda é tema controverso na literatura, não havendo estudos randomizados para uma avaliação definitiva.[14,38]

Embora a cirurgia transesfenoidal seja um tratamento de segunda linha, os dados sugerem que, quando realizada em centros de referência e por neurocirurgiões experientes, corresponde a um procedimento seguro e com potencial curativo para casos selecionados.

Radioterapia

A radioterapia é raramente necessária no tratamento dos prolactinomas, sendo reservada para os pacientes refratários ao tratamento medicamentoso com DA e ao tratamento cirúrgico, geralmente representados pelos tumores agressivos ou malignos.[14,23,24,38] Os prolactinomas representam uma das classes de tumores hipofisários mais radiorresistentes, apresentando taxas de normalização dos níveis de PRL em aproximadamente um terço dos pacientes nas séries de radioterapia (34,1% com radioterapia convencional e 31,4% com radioterapia estereotáxica).[38]

A radioterapia é associada a uma série de complicações, incluindo hipopituitarismo (deficiência de pelo menos um novo setor hormonal da adeno-hipófise pode ocorrer em até 50% dos pacientes ao longo de 10 a 20 anos pós-irradiação); lesão do nervo óptico; déficit neurológico; radionecrose cerebral; acidente cerebrovascular e neoplasia (benigna e maligna) intracraniana secundária.[14,17,38]

Outros tratamentos farmacológicos

Temozolomida, um agente alquilante oral de DNA, corresponde a um quimioterápico empregado no tratamento de adenomas hipofisários agressivos e carcinomas de hipófise desde 2006.[36] Apresenta moderado sucesso em alguns prolactinomas agressivos/malignos e resistentes aos DA, com relatos de casos evidenciando uma redução de 30% do volume tumoral em 50% dos pacientes tratados.[36]

Algumas séries reportam uma melhora significativa com normalização dos níveis de PRL, redução significativa do volume tumoral primário e desaparecimento de metástases.[36]

Existem vários protocolos de uso, porém o mais frequentemente descrito corresponde à administração de 150-200 mg/m^2 por dia durante 5 dias a cada 4 semanas.[14] A temozolamida age inserindo um grupo metila nas bases de DNA, principalmente a guanina. A baixa expressão da O(6)-metilguanina metiltransferase (MGMT), uma enzima de reparo de DNA responsável por remover os grupos metilas e, portanto, neutralizar o efeito da temozolamida, tem sido relacionada à melhor resposta do quimioterápico nesses pacientes.[36,39] Efeitos colaterais são esperados, como fadiga (60%), náusea/vômito (30%), além de mielossupressão (31%) e alteração de enzimas.[39] Infelizmente, muitos desses tumores agressivos que apresentam resposta inicial favorável manifestam escape dos efeitos supressivos da medicação após 0,5 a 2,5 anos.[17,35,36]

Análogos da somatostatina de primeira geração (octreotida e lanreotida) são ineficazes no tratamento dos prolactinomas, com poucos relatos de casos demonstrando sucesso no tratamento quando associados à cabergolina em casos de adenomas resistentes à DA.[17,36] Embora todos os receptores de somatostatina (SSTR) estejam presentes nos prolactinomas, o mais frequentemente encontrado é o SSTR5.[36]

Dessa forma, há uma vantagem teórica do uso do pasireotide, análogo da somatostatina de segunda geração e com maior afinidade ao SSTR5, para o tratamento dos prolactinomas agressivos e resistentes aos DA.[17,36]

O uso de moduladores seletivos do receptor de estrogênio (SERM) tem sido relatado em alguns casos de prolactinomas resistentes aos DA, porém com resultados limitados e inconclusivos.[36] Outras terapias promissoras, como inibidores de tirosina quinase, imunoterapia, inibidores do alvo da rapamicina em mamíferos (mTOR), dentre outras, encontram-se em estudo.[36]

Prolactinomas gigantes

Não há um consenso com relação à definição de prolactinomas gigantes, mas o mais utilizado corresponde a adenomas hipofisários > 4 cm associados a níveis de PRL > 250 µg/L (usualmente > 1.000 µg/L) **(Figura 3)**.[40] Embora sua real prevalência não seja conhecida, estima-se que varia entre 0,5% a 4,4% de todos os tumores hipofisários.[40] Os prolactinomas gigantes ocorrem mais comumente em homens (relação homens/mulheres de 6,5/1), têm comportamento mais agressivo e podem ser encontrados em pacientes com idade média de 42 anos.[40]

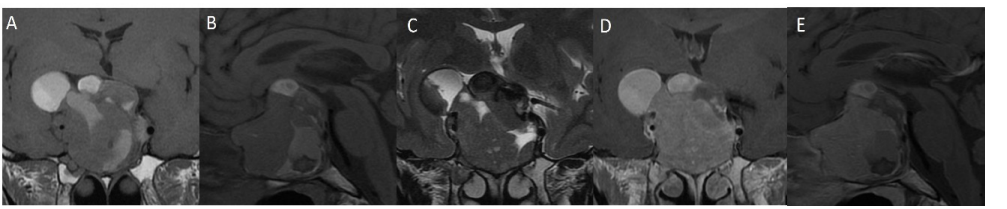

Figura 3. Ressonância magnética mostrando prolactinoma gigante com expansão supra, infra e parasselar. A lesão é isointensa em T1 (A e B cortes coronal e sagital), com áreas espontaneamente hiperintensas. Nas sequências pesadas em T2 (C), a lesão também se mostrou isointensa, com áreas hiperintensas. Nas sequências pós-contraste (D e E), a lesão apresentou realce pós-contraste. O aspecto sugere degeneração hemorrágica (apoplexia)
Arquivo pessoal dos autores.

Os prolactinomas gigantes causam manifestações clínicas associadas a sintomas de massa e hiperprolactinemia, conforme descrito anteriormente. Revisão sobre o tema na literatura aponta que déficit visual ocorre em 71% dos casos, cefaleia em 59% e hipopituitarismo em 33%, embora a avaliação endocrinológica hipofisária não tenha sido avaliada ou reportada em alguns artigos.[41] Apresentações clínicas atípicas podem ocorrer, refletindo o tamanho e a extensão tumoral aos tecidos adjacentes. Extensões supra, infra, para, antero e retrosselares são observadas em até 60% dos casos reportados.[41] Hidrocefalia e rinorreia liquórica espontânea são complicações raras, esta última, em geral, induzida pelo tratamento cirúrgico ou medicamentoso, associada a uma diminuição rápida do tamanho tumoral.[41]

Os DA correspondem à terapia de primeira linha em casos de prolactinomas gigantes mesmo que haja efeitos compressivos, devido às altas taxas de resposta, inclusive com redução do volume tumoral após poucos dias de início da medicação.[40] Em séries coletadas que totalizavam 97 episódios de prolactinomas gigantes (73 homens e 24 mulheres), o tratamento com DA normalizou os níveis de PRL em 60% dos casos, reduziu o tumor significativamente (definido por diminuição ≥ 30% no diâmetro) em 74% e melhorou o déficit visual em 96%.[41]

É necessária observação cuidadosa durante o tratamento medicamentoso, pois há o risco de complicações, em geral relacionadas à redução do volume tumoral, desmascarando erosões ósseas previamente tamponadas.[40,41] Portanto, deve-se atentar para o risco de pneumoencéfalo,

rinorreia liquórica, meningite e apoplexia.[40,41] Importante ressaltar que o tratamento com DA em casos de prolactinoma gigante geralmente é crônico, não havendo relatos na literatura de retirada medicamentosa bem-sucedida.[40,41]

Em casos de prolactinomas gigantes resistentes ou intolerantes aos DA, tratamentos alternativos são necessários, como cirurgia, em geral citorredutora (*debulking*), radioterapia e/ou temozolomida. Pacientes com hipogonadismo persistente, sem controle bioquímico e com volume tumoral residual, porém sem efeito de massa, devem ter sua reposição hormonal sexual avaliada.[40] Há o risco de a estrogenoterapia na mulher e da testosterona (e sua consequente aromatização) no homem induzirem um crescimento tumoral. Logo, cada caso deve ser individualizado, e, optando-se pela reposição, é necessário o acompanhamento com níveis de PRL e RM de hipófise.

Prolactinomas na gestação

O acompanhamento da gestante com prolactinoma requer um cuidado especial, pois há o risco de crescimento tumoral (e efeitos compressivos), relacionado aos altos níveis de estrogênio e/ou à descontinuação medicamentosa dos DA, além da preocupação com a possibilidade de malformação fetal associada aos próprios DA.[17] O risco da expansão tumoral durante a gravidez é diretamente proporcional ao tamanho do adenoma, ocorrendo em 2,5% dos microprolactinomas, 18,1% dos macroprolactinomas sem cirurgia ou irradiação prévia e 4,7% dos macroadenomas submetidos à cirurgia e/ou irradiação.[42]

Pacientes com microprolactinomas ou macroprolactinomas intrasselares (afastados do quiasma óptico) podem ter o tratamento com DA descontinuado após a confirmação da gestação, necessitando acompanhamento clínico trimestral, sempre informando e questionando a gestante quanto a possíveis sintomas relacionados à expansão tumoral, como cefaleia importante e alterações visuais.[17,42] As pacientes com macroprolactinomas expansivos/invasivos devem ter a manutenção do DA avaliada pelo especialista individualmente.[17] Nesses casos, é importante o acompanhamento clínico mensal e neuro-oftalmológico (campimetria manual) a cada 3 meses.[17] A dosagem de PRL não é recomendada, pois seus níveis são variáveis durante a gestação e, caso haja aumento importante, pode não haver correlação com o tamanho do adenoma.[42] A paciente deve ser orientada quanto aos sinais e sintomas de alarme compatíveis com crescimento tumoral, como cefaleia e déficit visual, e, caso presentes, deve-se solicitar RM hipófise (sem contraste).[17] Deve-se reintroduzir o DA caso o crescimento do adenoma seja evidenciado.

Devido à maior experiência de uso, a bromocriptina é considerada a primeira opção terapêutica na mulher com prolactinoma e deseja engravidar, pois geralmente leva à redução tumoral e ao alívio dos sintomas.[17] A cabergolina deve ser considerada em casos de intolerância ou resistência a bromocriptina.[17] Embora tenha sido demonstrado que a bromocriptina é capaz de atravessar a placenta em estudos humanos e a cabergolina em estudos em animais, ensaios envolvendo mais de 6 mil gestantes com a primeira medicação e mil com a segunda não revelaram maior risco de malformações ou desfechos adversos durante a gravidez.[42] Em contraste com esses estudos, Hurault-Delaurue *et al.* reportaram que 183 mulheres (0,3%) que receberam DA em algum momento da gestação (75% no primeiro trimestre), quando comparadas a um grupo-controle, tiveram um aumento de risco de partos prematuros e abortamentos, além de um aumento não significativo de malformações, embora sem diferença no desenvolvimento psicomotor em 9 e 24 meses.[43]

A neurocirurgia, preferencialmente durante o segundo trimestre, está indicada em casos de macroprolactinomas com efeitos compressivos e refratários à terapia medicamentosa.[17] Caso a gestação esteja próxima do termo, o parto deve ser discutido com a equipe obstétrica.

Não há dados que sugiram que a amamentação estaria associada a um aumento do adenoma; logo, está permitida nas mulheres com prolactinomas.[42]

Conclusão

Em resumo, a hiperprolactinemia é uma alteração frequente na prática médica, podendo ser causada por diversos fatores (fisiológicos, medicamentosos e patológicos). Dentre as causas patológicas, o prolactinoma é a principal. A investigação da hiperprolactinemia representa um desafio diagnóstico devido às diversas armadilhas inerentes à interpretação dos exames e às várias etiologias possíveis. O tratamento de primeira escolha nos prolactinomas é, em geral, medicamentoso (DA), independentemente do tamanho do adenoma. A cabergolina é a droga preferencialmente utilizada, tendo um bom perfil de segurança e tolerabilidade, embora haja potenciais efeitos adversos graves que devem ser monitorados pelo médico assistente, como doenças cardíacas orovalvares e distúrbios psiquiátricos. O tratamento cirúrgico primário pode ser indicado em casos específicos individualmente. Em casos de pacientes com resistência ou intolerância aos DA, outras terapias estão indicadas, como neurocirurgia, radioterapia e medicamentos alternativos (temozolomida).

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