Universidade Federal do Maranhão
Pró-Reitoria de Pesquisa e Pós-Graduação
Programa de Pós-Graduação em Saúde Materno Infantil –
Mestrado Acadêmico

CÂNCER DE TIRÓIDE EM PACIENTES COM ACROMEGALIA: UM ESTUDO CASO-CONTROLE

Maíra Cristina Carvalho dos Santos

São Luís
2012

Maíra Cristina Carvalho dos Santos

CÂNCER DE TIRÓIDE EM PACIENTES COM ACROMEGALIA: UM ESTUDO CASO-CONTROLE

Dissertação apresentada ao Programa de Pós-Graduação em Saúde Materno Infantil da Universidade Federal do Maranhão, para a obtenção do Título de Mestre em Saúde Materno-Infantil.

Área de concentração: Medicina II

Orientador: Prof. Dr. Manuel dos Santos Faria

Coordenador: Prof. Dra. Maria Bethânia da Costa Chein

São Luís

2012

Santos, Maíra Cristina Carvalho dos

Câncer de tiróide em pacientes com acromegalia: um estudo caso-controle/Maíra Cristina Carvalho dos Santos. - São Luís, 2012.

62f.

Orientador: Prof. Dr. Manuel dos Santos Faria.

Dissertação (Mestrado) – Mestrado em Saúde Materno-Infantil, Universidade Federal do Maranhão, 2012.

1. Acromegalia e câncer. 2. IGF-1 e câncer. 3. Tiróide e acromegalia. 4. GH e câncer. I. Título.

CDU 616.693

Maíra Cristina Carvalho dos Santos

CÂNCER DE TIRÓIDE EM PACIENTES COM ACROMEGALIA: UM ESTUDO CASO-CONTROLE

Dissertação apresentada ao Programa de Pós-Graduação em Saúde Materno Infantil da Universidade Federal do Maranhão, para a obtenção do Título de Mestre em Saúde Materno-Infantil.

A Banca Examinadora da Dissertação de Mestrado apresentada em sessão pública, considerou a candidata aprovada em: _____/_____/_____.

_____
Prof. Dr. Manuel dos Santos Faria (Orientador)
(Universidade Federal do Maranhão)

_____
Prof. Dr. Heraldo Mendes Garmes
(Universidade Estadual de Campinas)

_____
Prof. Dra. Maria do Rosário da Silva Ramos Costa
(Universidade Federal do Maranhão)

_____
Prof. Dra. Flávia Castello Branco Vidal Cabral
(Universidade Federal do Maranhão)

São Luís

2012

Aos meus pais,
base e início de tudo.
Ao meu esposo Rodrigo, companheiro e
porto seguro em todos os momentos.
Aos meus filhos Diego e Carolina, fonte
revigorante de energia após cada dia de
trabalho.

AGRADECIMENTOS

A Deus, por minha vida.

À minha família, meus pais, marido e filhos, por todo carinho e estímulo que me dedicam.

Ao Prof. Dr. Manuel dos Santos Faria, pelo incentivo, paciência e orientação na realização desta pesquisa.

À cada membro desta equipe, sem a qual este trabalho não seria realidade: Gilvan Nascimento, Viviane Carvalho, Conceição Parente, Ana Gisélia Nascimento, Maria Honorina Lopes, Alice Alves, Emílio Carneiro, Renan Montenegro, Lucio Vilar, Mônica Albano, Adriana Sá, Marinildes Teles e Natália Coelho.

“Quando vires um homem bom, tenta imitá-lo; quando vires um homem mau, examina-te a ti mesmo.”

Confúcio

RESUMO

Vários estudos têm associado acromegalia a um risco aumentado de tumores benignos e malignos. Enquanto bócios simples e multinodulares são achados comuns em acromegálicos, a prevalência de câncer de tireóide é incerta. O objetivo deste estudo foi estimar a prevalência de câncer de tireóide em uma série de pacientes com acromegalia de três hospitais do nordeste brasileiro. A metodologia utilizada incluiu a análise morfológica, citológica e histopatológica da tiróide de pacientes acromegálicos e voluntários com mais de 18 anos, pareados por idade e sexo e com nódulo (s) ≥ 1 cm. Foram avaliados 124 pacientes com acromegalia, incluindo 76 mulheres (61,3%) e 48 homens (38,7%), com idade média de 45,1 anos. Ao estudo ultrassonográfico da tiróide evidenciou-se normalidade em 31 casos (25%), 25 tinham bócio difuso (20,1%), 67 apresentavam nódulos (54%) e um agenesia do lobo direito (0,8%). Trinta e seis pacientes foram submetidos a biópsia aspirativa por agulha fina (PAAF) de seus nódulos e 9 casos de carcinoma papilífero foram encontrados (7,2%). O grupo controle consistiu de 263 indivíduos, 156 do sexo feminino (59,3%) e 107 do sexo masculino (40,7%), com idade média de 44,7 anos. Na avaliação ultrassonográfica, 96 apresentavam nódulos (36,5%). Destes, 13 foram puncionados e 2 casos de carcinoma papilífero foram encontrados (0,7%). Estes resultados conferiram um odds ratio de 10,21 (p = 0,0011, IC 95% 2,17-48,01). Estes resultados demonstraram uma prevalência aumentada de câncer de tiróide, estatisticamente significativa, quando comparado ao nosso grupo controle. Desta forma, sugere-se que pacientes acromegálicos devam rotineiramente ser submetidos a exame ultrassonográfico da tiróide, seguido por PAAF de nódulos quando indicado.

Palavras-chave: acromegalia e câncer, IGF-1 e câncer, tiróide e acromegalia, GH e câncer.

ABSTRACT

Several studies have associated acromegaly with an increased risk of benign and malignant tumors. While simple and multinodular goiters are common findings in acromegaly, the prevalence of thyroid cancer is uncertain. The objective of this study was to estimate the prevalence of thyroid cancer in a series of acromegalic patients from three hospitals in northeast of Brazil. The methodology used included morphological, cytological and histological thyroid analysis of acromegalic patients and volunteers over 18 years, matched for age and sex and with nodule (s) ≥ 1 cm. The subjects of this study were 124 acromegalic patients, including 76 females (61.3%) and 48 men (38.7%), with a mean age 45.1 years. Results of the study showed that thyroid ultrasonography was normal in 31 cases (25%), 25 had diffuse goiter (20.1%), 67 had nodules (54%) and one agenesis of the right lobe (0.8%). Thirty six patients underwent fine needle aspiration biopsy (FNAB) of their nodules and 9 cases of papillary cancer were found (7.2%). The control group consisted of 263 subjects, 156 females (59.3%) and 107 males (40.7%), mean age 44.7 years. In ultrasound assessment, 96 had nodules (36.5%). Of these, 13 were punctured and 2 cases of papillary carcinoma were found (0.7%). These results gave an odds ratio of 10.21 ($p = 0.0011$, 95% CI 2.17 to 48.01). These findings demonstrate an increased prevalence of thyroid cancer, statistically significant when compared to our control group. Thus, it is suggested that acromegalic patients should be routinely submitted to thyroid ultrasound evaluation, followed by FNAB of nodules when indicated.

Keywords: acromegaly and cancer, IGF-1 and cancer, thyroid and acromegaly, GH and cancer.

LISTA DE TABELAS

LISTA DE FIGURAS

SUMÁRIO

1 INTRODUÇÃO

Acromegalia é um distúrbio endócrino raro causado por secreção excessiva de hormônio do crescimento (GH), tendo como principal etiologia um adenoma hipofisário produtor de GH. Os efeitos de GH são mediados em grande parte pelo estímulo à produção do fator de crescimento insulina-símile I (IGF-1) (MELMED, 2006).

Está associada com mortalidade prematura causada por doenças cardiovasculares, respiratórias e metabólicas, bem como risco aumentado de certas malignidades (CLAYTON et al., 2011; COLAO et al., 2004; MELMED, 2006; MELMED et al., 2009).

A associação entre crescimento tumoral e GH/ IGF-1 está bem estabelecida (COHEN et al., 2000; RENEHAN & BRENNAN, 2008). No entanto, não há consenso sobre o risco aumentado de desenvolver câncer em pacientes com acromegalia (MELMED, 2001; ORME et al., 1998).

Evidências contraditórias sugerem que acromegalia está associada com um risco aumentado de neoplasia de cólon (MELMED, 2001; TERZOLO et al., 2005; ROKKAS et al., 2008). Possíveis mecanismos envolvidos neste excesso de risco incluem um efeito trófico do IGF-1 sobre a proliferação de células epiteliais (CATS et al., 1996), além de expressão reduzida do gene do receptor ativado por proliferadores de peroxissoma (PPAR) (BOGAZZI et al., 2003).

Em pacientes com acromegalia há uma alta prevalência de bócio, especialmente bócio nodular atóxico (GASPERI et al., 2002; RUCHALA et al., 2009). Cheung e Boyages (1997) encontraram em 37 indivíduos com acromegalia, uma incidência global de 92% de bócio. Estes achados sugerem que no início do curso da doença, ocorre bócio difuso. Entretanto, o aumento da prevalência de câncer de tiróide nestes pacientes ainda permanece incerta.

Parte desta dificuldade em determinar a verdadeira incidência de câncer nesta população resulta da relativa raridade da acromegalia. Além disso, somente após o avanço no tratamento da doença em si e de suas complicações, estes pacientes estão sobrevivendo tempo suficiente para atingir idade de maior risco para câncer (JENKINS & BESSER, 2001).

O objetivo deste estudo é determinar a prevalência de câncer de tiróide neste grupo de pacientes com acromegalia e comparar os resultados com um grupo controle.

2 FUNDAMENTAÇÃO TEÓRICA

Acromegalia é uma doença caracterizada por um progressivo desfiguramento somático com aumento de partes moles das extremidades e extensas manifestações sistêmicas, secundárias a produção excessiva de hormônio do crescimento (GH) na vida adulta (RIBEIRO et al., 2003). Acomete tanto homens quanto mulheres, variando de 0,7 a 1,8 nas diferentes séries, com discreto predomínio para o sexo feminino (CZEPIELEWSKI; ROLLIN, 2004). É uma doença rara com prevalência de aproximadamente 40 a 70 pacientes por milhão e a incidência, de três a quatro pacientes ao ano por milhão de indivíduos, com pico de incidência na quinta década. Apresenta elevada taxa de morbi-mortalidade a longo prazo se não tratada (BENGTSSON et al, 1988; COLAO et al., 2004).

Uma das primeiras descrições clínicas desta doença data de 1864, quando o crânio de uma mulher afetada por prosopectasia (derivado das palavras gregas prosopon, face, e ektasis, alargamento), foi descrito por Andrea Verga (COLAO et al., 2004). Em 1881, Vicenzo Brigidi relatou hipófise aumentada e hipertrofiada em autópsia de paciente com achados clínicos compatíveis com acromegalia. O termo “acromegalia” (extremidades grandes) só foi incorporado em 1886 por Pierre Marie, quando descreveu dois pacientes com as características típicas da síndrome. Posteriormente, ao longo do século seguinte, foram esclarecidas as associações da hipófise com a acromegalia e a produção do GH e das somatomedinas - IGFs (CZEPIELEWSKI; ROLLIN, 2004).

A principal etiologia da doença é um adenoma hipofisário produtor do GH, representando cerca de 98% dos casos. Raramente encontramos carcinoma hipofisário, secreção ectópica do hormônio liberador do GH (GHRH) ou secreção ectópica do próprio GH (COLAO et al., 2004).

O diagnóstico de acromegalia é feito tardiamente, em média oito anos após o início dos sintomas, devido sua evolução lenta e progressiva. Este atraso diagnóstico torna-se preocupante na medida em que a acromegalia está associada a uma morbimortalidade significativa, reduzindo a expectativa de vida com aumento de mortalidade de duas a quatro vezes. Ele pode ser sugerido apenas com a inspeção do paciente, que apresenta aumento das mãos e dos pés e modificações

fisionômicas grosseiras, além de queixas como cefaléia, fadiga, intolerância ao calor e ganho de peso (CZEPIELEWSKI; ROLLIN, 2004).

Porém, o diagnóstico deve ser confirmado bioquimicamente através dos níveis de IGF-1 elevado para sexo e idade e pela não supressão do GH no teste oral de tolerância a glicose - TOTG (GH superior a 1 mcg/L após administração oral de 75 g de glicose, dosando-se o GH nos tempos 0, 30, 60 e 90 minutos), segundo o consenso de 2000. Exames radiológicos podem ser realizados em busca da etiologia da doença (CZEPIELEWSKI; ROLLIN, 2004).

As manifestações clínicas da acromegalia decorrem de efeitos sistêmicos do excesso de GH/ IGF-1, de efeitos locais dependentes do volume tumoral, como cefaléia e alteracão visual; e de disfunções na secreção de outros hormônios hipofisáros, como hiperprolactinemia e hipopituitarismo. Sistemicamente, a acromegalia causa uma visceromegalia generalizada, levando a alterações cardíacas, respiratórias, metabólicas, osteoarticulares e outras consequências endócrinas como o bócio. Aumento de volume da tiróide é clínica e ultrassonograficamente detectado em 25% a 92% dos pacientes acromegálicos (COLAO et al., 2004). Os mecanismos que envolvem a hiperplasia de tecido tiroideano são dependentes de efeitos sinérgicos do excesso de GH/ IGF-1 e de TSH sobre a célula folicular tiroideana (MISAKI et al., 1988; MINUTO et al., 1989). Estes efeitos fazem com que haja secreção de T4 relativamente independente de TSH. Assim, em pacientes acromegálicos não tratados observam-se níveis normais de T4 e níveis reduzidos de TSH basal após estímulo com TRH, além de ocorrer correlação inversa desses níveis com os de IGF-1 circulantes (CZEPIELEWSKI; ROLLIN, 2004).

Cheung et al (1997) sugerem que inicialmente, no curso da doença, ocorre o bócio difuso sob ação conjunta de TSH e IGF-1. Subsequentemente, autonomia da glândula e formação de nódulos ocorreria pelo estímulo de IGF-1, sendo o TSH dispensável neste momento. Assim, o TSH seria apenas um fator permissivo, pois sua ausência não permite o crescimento da glândula (MARCHISOTTI et al., 2005).

Na maioria das vezes o bócio é multinodular, benigno e não provoca alteração funcional da tiróide. Porém, o risco de desenvolvimento destes nódulos tiroideanos cresce com o aumento da duração da doença (CHEUNG & BOYAGES, 1997).

Histologicamente, tem sido descrito tecido tiroideano com aspecto coloidal, hiperplásico e adenomatoso (COLAO et al., 2004).

Balkany e Cushing (1995) sugeriram que tumores da tiróide poderiam ser estimulados pelo aumento dos níveis circulantes de IGF-1. Sua suposição é favorecida pelo fato de existirem três vezes mais receptores de IGF-1 em tecido neoplásico tiroideano do que em tecido normal. Além disso, IGF-1 promoveu a replicação do DNA de células tiroideanas cancerosas (MARCHISOTTI et al., 2005).

Recentemente, vários estudos epidemiológicos têm sugerido que o nível elevado de IGF-1 aumenta o risco de câncer na população em geral, enquanto que altos níveis da principal proteína ligadora de IGF (IGFBP-3) estão associados à redução do risco, sugerindo um papel protetor da IGFBP-3, esta promove apoptose e interrompe a proliferação de células tumorais (MANOUSOS et al., 1999; MA et al., 1999; JENKINS et al., 2000). O IGF-1 parece participar de uma forma permissiva em conjunto com oncoproteínas nas fases de promoção e progressão do processo de tumorigênese. O sistema IGF-1/ IGF-1R influencia a progressão de células cancerosas pela presença de adesão e migração das células, e da angiogênese nos tecidos tumorais e nos tecidos ao redor. Em adição a suas funções endócrinas, IGF-1 é também sintetizado localmente em vários tecidos; exercendo ação autócrina / parácrina em células e tecidos (MARCHISOTTI et al., 2005).

Os cânceres constituem a terceira causa de mortalidade em pacientes com acromegalia. E os tumores digestivos constituem as neoplasias mais frequentemente relacionadas com esta doença. No total, câncer de tiróide constitui 3,1% dos eventos malignos em acromegalia, incidência, esta, significativamente aumentada para 3,3% no estudo de Baris et al (2002).

A prevalência deste câncer dentre os acromegálicos vem aumentando consideravelmente nos últimos estudos, chegando a uma prevalência de 5,5% no estudo de HERRMANN et al. (2004) e de 5,6% no de TITA et al. (2005). Já a incidência de câncer de tiróide na população geral é pequena, menor que 1%, variando em diferentes achados epidemiológicos de 1,2 a 2,6 por 100000 homens e de 2,0 a 3,8 por 100000 mulheres (GUIMARÃES, 2003). O que nos mostra a importância de pesquisarmos este câncer entre os pacientes com acromegalia.

3 OBJETIVOS

3.1 Geral

Determinar a prevalência de carcinoma de tiróide em grupo de pacientes com acromegalia e comparar com grupo controle.

3.2 Específicos

a) Avaliar alterações ultrassonográficas e citológicas na amostra em estudo;
b) Estimar a prevalência de câncer de tiróide em pacientes com acromegalia;
c) Comparar os dados encontrados nos pacientes acromegálicos com os do grupo-controle.

4 METODOLOGIA

4.1 Tipo de estudo

Transversal, analítico, do tipo caso-controle.

4.2 Período do estudo

De 2006 a 2010.

4.3 Local de realização do estudo

Serviço de Endocrinologia do Hospital Universitário Unidade Presidente Dutra da Universidade Federal do Maranhão (UFMA), Hospital Universitário Walter Cantídio da Universidade Federal do Ceará (UFC) e Hospital das Clínicas da Universidade Federal de Pernambuco (UFPE).

4.4 Critérios de inclusão

Participaram do estudo, pacientes que estiveram em acompanhamento nos serviços de Endocrinologia dos Hospitais Universitários dos centros citados, que forneceram termo de consentimento livre e esclarecido, com idade superior a 18 anos, de ambos os sexos, com diagnóstico clínico e bioquímico de acromegalia (níveis elevados de IGF-1 pareados para sexo e idade, níveis de GH maiores que 1ng/mL, após teste oral de tolerância a 75 g de glicose – TOTG e identificação de

adenoma hipofisário na ressonância magnética de sela túrcica). O grupo controle foi composto por voluntários da população em geral, sendo pareados por sexo e idade com o grupo de estudo, e que também forneceram termo de consentimento livre e esclarecido, com idade superior a 18 anos.

4.5 Desenho do estudo

Todos os pacientes foram convidados para participar da pesquisa e aqueles que aceitaram participar assinaram o Termo de Consentimento Livre e Esclarecido (TCLE) (APÊNDICE).

Todos os pacientes com diagnóstico de acromegalia e os pacientes do grupo-controle foram submetidos à ultrassonografia da tiróide. Aqueles pacientes que apresentaram nódulos maiores ou igual a 1 cm à ultrassonografia da tiróide foram submetidos à punção aspirativa com agulha fina (PAAF). Todo o material obtido pela PAAF em ambos os hospitais foi analisado pelo mesmo médico patologista. Diante de um exame citológico suspeito para malignidade ou de malignidade confirmada, os pacientes foram submetidos à tireoidectomia, e posterior confirmação diagnóstica através de exame histopatológico das espécimes obtidas.

O GH e IGF-1 foram dosados utilizando-se ensaio de quimioluminescência (Immulite® 1000).

A ultrassonografia da tireóide foi realizada usando equipamento MEDISON CO., LTD (KOREA®), com transdutor linear de 7,5 MHz. O volume tireoidiano foi calculado pela fórmula de De Chiro e Nelson (π/6 x comprimento x largura x espessura) para cada lobo. A PAAF foi realizada utilizando-se agulha 21G (30 x 0,8 mm BD) conectada a uma seringa descartável de 10 ml, sem pressão negativa, guiada por transdutor linear de 7,5 MHz. As lâminas foram fixadas em álcool 96° ou secas ao ar, e posteriormente coradas. Utilizou-se hematoxilina-eosina e/ou Papanicolaou para aquelas fixadas em álcool, e Giemsa para as lâminas secas ao ar.

Todos os pacientes com diagnóstico de câncer após tireoidectomia tiveram suas lâminas revisadas por dois patologistas. Nenhum dos pacientes com câncer

tinha fatores de risco adicionais para carcinoma diferenciado de tiróide, com exceção de um submetido a radioterapia.

4.6 Análise estatística

Para a análise dos dados utilizou–se a estatística descritiva (média, desvio padrão, percentual); os testes estatísticos $\chi 2$, Exato de Fisher para as variáveis classificatórias e o teste t de student para as variáveis numéricas.

Para o critério de determinação de significância adotou-se o nível de 5%. Quanto à análise estatística, esta foi processada pelo software estatístico BioEstat, versão 5.0.

4.7 Aspectos éticos

O trabalho foi aprovado pelo Comitê de Ética em Pesquisa do Hospital Universitário da Universidade Federal do Maranhão (CEP-HUUFMA) conforme Parecer Consubstanciado nº 356/06.

5 RESULTADOS

Foram avaliados 124 pacientes com acromegalia, dos quais 76 (61,3%) do sexo feminino e 48 (38,7%) do sexo masculino, com idade variando de 18 a 77 anos (média 45,1 ± 13,4 anos) (tabela 1). No estudo ultrassonográfico, 31 (25%) pacientes apresentaram tiróide normal, 25 (20,1%) bócio difuso, 67 (54%) nódulos e um (0,8%) agenesia do lobo direito (Figura 1, tabela 2). Trinta e seis pacientes (29%)

apresentaram nódulos tiroideanos sólido e/ou misto com tamanho maior ou igual a 1 cm, sendo todos puncionados.

Foram encontrados 9 (7,25%) casos de câncer, todos do tipo papilífero (3 homens e 6 mulheres, com idade média de 50,7 ± 10,8 anos) (Figura 2, tabelas 2 e 3). No grupo acromegálico sem câncer (115 pacientes) a idade média foi de 44,6 ± 13,5 anos, dos quais 45 (39,1%) eram do sexo masculino e 70 (60,8%) do sexo feminino (tabela 2).

Tabela 1 - Características demográficas dos participantes (n=387)

Variável	Grupo acromegálico	Grupo controle	P
Idade (média ± DP) (anos)	45,1 ± 13,4	44,7 ± 13,4	ns*
Masculino (n/ %)	48 (38,7%)	107 (40,7%)	ns*
Feminino (n/ %)	76 (61,3%)	156 (59,3%)	ns*
Total	124	263	

* Não significante

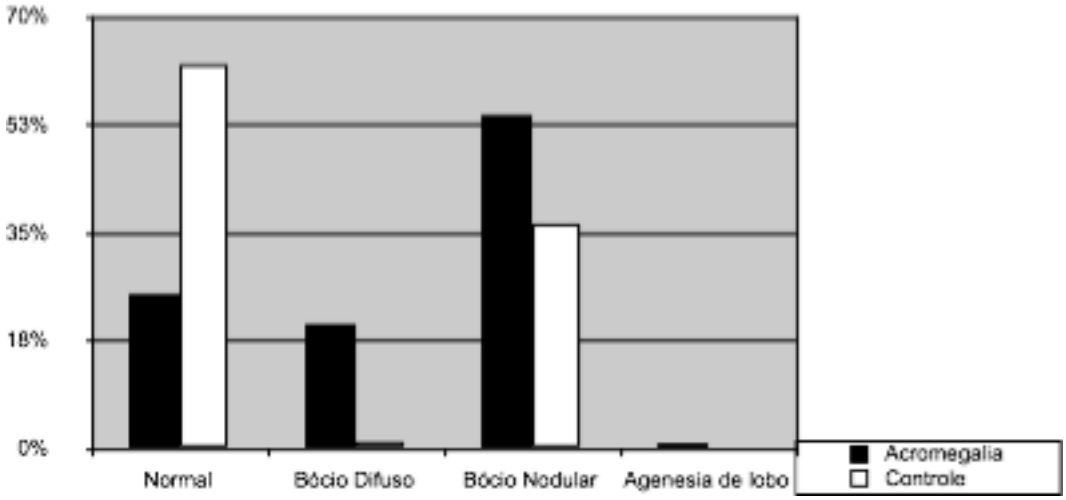

Figura 1 - Achados na ultrassonografia de tiróide (n=387)

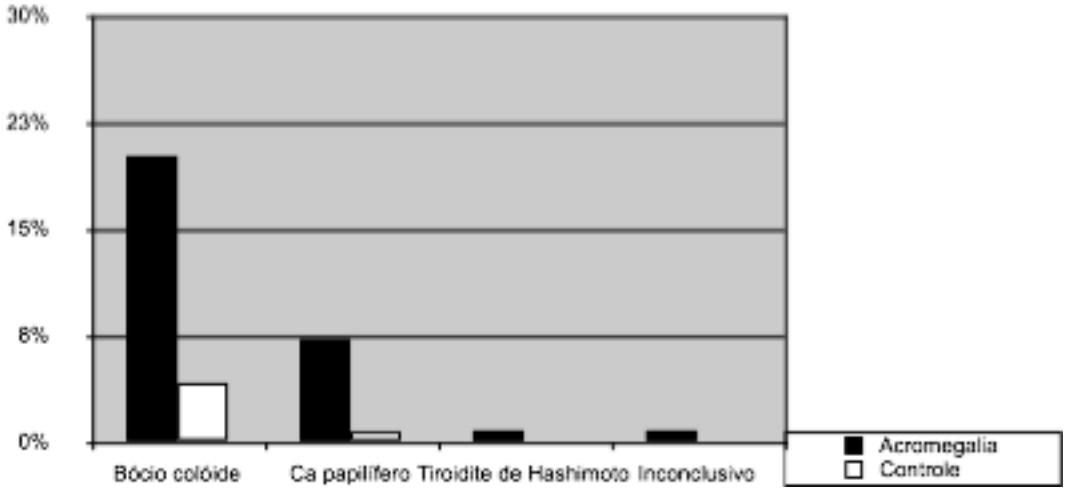

Figura 2 - Achados citológicos (n=49)

Tabela 2 - Características demográficas e avaliação tiroideana de 124 pacientes acromegálicos

Morfologia da tiróide (ultrassonografia)	
Normal	31 (25%)
Anormal	93 (75%)
Bócio difuso	25 (20.1%)
Bócio nodular	67 (54%)
Agenesia de lobo	1 (0.8%)
PAAF (em nódulos > 1cm)	36 (29%)
Benigno	26 (20.9%)
Inconclusivo	1 (0.8%)
Carcinoma papilífero	9 (7.2%)
Acromegálicos com câncer de tiróide	9 (7.2%)
Idade (média/ anos)	50.7*
Masculino (n/%)	3 (33.3%)*
Feminino (n/%)	6 (66.7%)*
Acromegálicos sem câncer de tiróide	115 (92.7%)
Idade (média/ anos)	44.6*
Masculino (n/%)	45 (39.1%)*
Feminino (n/%)	70 (60.8%)*

PAAF: punção aspirativa com agulha fina. * não significante

Tabela 3 - Características dos pacientes acromegálicos ao diagnóstico do carcinoma de tiróide (n=9)

Pct	Id (anos)	Sexo	RT	HF	Δt DX (anos)	RM	Histologia	Status acromegalia	%IGF-1 LSN
1	62	F	N	N	0	macroadenoma	papilífero	não controlada	125.6%
2	60	F	N	N	15	macroadenoma	papilífero	não controlada	117.7%
3	58	F	N	N	4	microadenoma	papilífero	controlada há 3 anos	< 100%
4	41	M	S	N	9	macroadenoma	papilífero	controlada há 5 anos	< 100%
5	56	F	N	N	5	macroadenoma	papilífero	não controlada	131.5%
6	56	F	N	N	1	macroadenoma	papilífero	não controlada	111.3%
7	32	M	N	N	5	macroadenoma	papilífero	controlada há 1 ano	< 100%
8	38	M	N	N	5	macroadenoma	papilífero	controlada há 1 ano	< 100%
9	54	F	N	N	0	microadenoma	papilífero	não controlada	N/D

RT: radioterapia; HF: história familiar; Δt DX: tempo do diagnóstico de acromegalia; LSN: limite superior da normalidade; N/D: não disponível.

O grupo controle foi constituído por 263 indivíduos, dos quais 156 (59,3%) do sexo feminino e 107 (40,7%) do sexo masculino, com idade entre 19-81 anos (média 44,7 ± 13,4 anos) (tabela 1). Ao exame ultrassonográfico, 96 (36,5%) indivíduos do grupo controle apresentavam nódulos de tamanhos variados, enquanto a maioria (62,36%) apresentava exame normal (Figura 1). Treze voluntários apresentaram nódulos tiroideanos sólido e/ou misto com tamanho maior ou igual a 1 cm, sendo todos puncionados, e dois casos de carcinoma papilífero encontrados (0,7%) (Figura 2).

Estes resultados conferiram um odds ratio de 10.21 (p = 0,0011, 95% CI 2.17 - 48.01) para câncer de tiróide nos pacientes com acromegalia (Tabela 4).

Tabela 4 - Prevalência de carcinoma de tiróide na amostra (n=387)

Variável	Grupo acromegálico	Grupo controle	Odds Ratio
Casos (n)	9 (7,2%)	2 (0,7%)	10.21 (CI 2,17-48,01)*
Idade (média/ anos)	50,7	39,5	
Masculino (n/ %)	3 (33,3%)	1 (50%)	
Feminino(n/ %)	6 (66,7%)	1 (50%)	

* p = 0.0011

6 REFERÊNCIAS

BALKANY, C.; CUSHING, G.W. An association between acromegaly and thyroid carcinoma. Thyroid, 5: 47-50, 1995.

BARIS, D. et al. Acromegaly and cancer risk: a cohort study in Sweden and Denmark. Cancer Causes Control, 13: 395-400, 2002.

BENGTSSON, B.A. et al. Epidemiology and long term survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984. Acta Med Scand, 223(4): 327, 1988.

BOGAZZI, F. et al. Changes in the expression of the peroxisome proliferator-activated receptor gamma gene in the colonic polyps and colonic mucosa of acromegalic patients. J Clin Endocrinol Metab, 88: 3938-42, 2003.

CATS, A. et al. Increased epithelial cell proliferation in the colon of patients with acromegaly. Cancer Res 56: 523-6, 1996.

CHEUNG, N.W.; BOYAGES, S.C. The thyroid gland in acromegaly: an ultrasonographic study. Clin Endocrinol (Oxf), 46: 545–549, 1997.

CLAYTON, P.E.; BANERJEE, I.; MURRAY, P.G.; RENEHAN, A.G. Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. Nat Rev Endocrinol, 7: 11-24, 2011.

COHEN, P.; CLEMMONS, D.R.; ROSENFELD, R.G. Does the GH-IGF-1 axis play a role in cancer pathogenesis? Growth Horm IGF Res, 10: 297-305, 2000.

COLAO, A. et al. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endo. Rev, 25: 102-152, 2004.

CZEPIELEWSKI, M. A.; ROLLIN, G. A. F. S. Acromegalia e gigantismo. In: LIBERMAN, B.; CURKIERT, A. Fisiologia e Fisiopatologia do hormônio do crescimento, São Paulo: Lemos, 2004. p. 337-360.

GASPERI, M.; MARTINO, E.; MANETTI, L.; AROSIO, M.; PORRETTI, S.; FAGLIA, G. et al. Prevalence of thyroid diseases in patients with acromegaly: results of an Italian multicenter study. J Endocrinol Invest, 25: 240-245, 2002.

GUIMARÃES, V. C. C. Câncer diferenciado da tireóide. In: FARIA, M. S. et al. Endocrinologia e Diabetes, Rio de Janeiro: MEDSI, 2003, v.1, p. 117-125.

HERRMANN, B. L. et al. Impact of disease activity on thyroid diseases in patients with acromegaly: basal evaluation and follow-up. Exp Clin Endocrinol Diabetes,112(5): 225-230, 2004.

JENKINS, P.J. et al. Insulin-like growth factor I and the development of colorectal neoplasia in acromegaly. J Clin Endocrinol Metab, 85: 3218-3221, 2000.

JENKINS, P.J.; BESSER, M. Clinical perspective: acromegaly and cancer: a problem. J Clin Endocrinol Metab, 86: 2935-41, 2001.

MA, J. et al. Prospective study of colorectal cancer risk in men and plasma level of insulin-like growth factor (IGF-1) and IGF-binding protein-3. J Natl Cancer Inst, 91: 620-625, 1999.

MANOUSOS, O. et al. IGF-1 and IGF-2 in relation to colorectal cancer. Int J Cancer, 83: 15-17, 1999.

MARCHISOTTI, F. G. et al. Acromegalia e doença tireoidiana: prevalência de câncer de tireóide. Arq Bras Endocrinol Metab, 49/5: 843-849, 2005.

MELMED, S. Acromegaly and cancer: not a problem? J Clin Endocrinol Metab, 86: 2929-2934, 2001.

MELMED, S. Medical progress: acromegaly. N Engl J Med, 355: 2558–2573, 2006.

MELMED, S. Guidelines for Acromegaly Management: An Update. J Clin Endocrinol Metab, 94: 1509-17, 2009.

ORME, S.M. et al. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab, 83: 2730-4, 1998.

RENEHAN, A.G.; BRENNAN, B.M. Acromegaly, growth hormone and cancer risk. Best Pract Res Clin Endocrinol Metab, 22: 639-57, 2008.

RIBEIRO, V.; MOTENEGRO, A.C.; BANDEIRA, F. Acromegalia e gigantismo. In: FARIA, M. S. et al. Endocrinologia e diabetes. Rio de Janeiro: MEDSI, 2003. v 1. p. 117-125.

ROKKAS, T. et al. Risk of colorectal neoplasm in patients with acromegaly: a meta-analysis. World J Gastroenterol, 14: 3484–3489, 2008.

RUCHALA, M.S. et al. The occurrence of thyroid focal lesions and a need for fine needle aspiration biopsy in patients with acromegaly due to an increased risk of thyroid cancer. Neuro Endocrinol Lett, 30: 382-386, 2009.

TERZOLO, M. et al.: Colonoscopic screening and follow-up inpatients with acromegaly: a multicenter study in Italy. J Clin Endocrinol Metab, 90: 84-90, 2005.

TITA, P. et al. High prevalence of differentiated thyroid carcinoma in acromegaly. Clinical Endocrinology 63: 161-167, 2005.

7 APÊNDICE

Termo de Consentimento Livre e Esclarecido

UNIVERSIDADE FEDERAL DO MARANHÃO
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM SAÚDE MATERNO INFANTIL

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Nome do Projeto: Câncer de Tiróide em pacientes com acromegalia: um estudo caso-controle.
Coordenador: Manuel dos Santos Faria
Mestranda: Maíra Cristina Carvalho dos Santos

O objetivo desta pesquisa é avaliar se a doença Acromegalia aumenta a chance do paciente ter um Câncer de Tiróide e, assim, determinar o número de casos em nossos pacientes. Para confirmar a importância deste trabalho é necessária a comparação com um grupo controle, que são indivíduos que não apresentam a doença Acromegalia. Nós estamos convidando você a participar desta pesquisa, porque você faz parte de um grupo da população semelhante ao grupo do estudo. Nós iremos fazer uma avaliação, com objetivo de identificar alguma alteração em sua glândula tireóide. Para isto, solicitamos que seja coletada uma pequena amostra do seu sangue, para avaliar as taxas dos hormônios produzidos pela tireóide. Nós também solicitaremos uma ultrassonografia da tiróide para determinar a presença de nódulos. Caso você apresente nódulo(s) igual ou maior que 1 cm na sua tiróide, você será submetido a uma punção guiada por ultrassonografia, na qual será retirada uma amostra do nódulo para avaliar a sua natureza, conforme recomendação das Sociedades Nacionais e Internacionais de Endocrinologia. Caso apresente resultados alterados nos exames hormonais e/ou na punção de tiróide,

você será encaminhado ao Serviço de Endocrinologia do Hospital Universitário Presidente Dutra.

PROCEDIMENTOS

Abaixo estão descritos os procedimentos a serem seguidos para aqueles que concordarem em participar do estudo:

Avaliação médica;

Coleta de sangue, em jejum de 8 horas, que será realizado através de técnica estéril/limpa pelos funcionários do laboratório do HUUPD.

Ultrassonografia será realizada no Centro de Diagnóstico Médico, no Renascença Medical Center, pela médica Conceição Veiga Parente, a qual atende toda quarta sexta-feira no período da tarde a partir das 14 horas. O encaminhamento será entregue após a consulta.

Punção Aspirativa por Agulha Fina (PAAF) da Tiróide guiada por Ultrassonografia naqueles com nódulos, conforme descrito acima. Será realizada às quartas-feiras em local descrito no item 3, pela médica Conceição Veiga Parente e auxílio do médico residente em Endocrinologia do serviço de Residência médica em Endocrinologia do HUUFMA, conforme agendamento prévio.

RISCOS

Os riscos possíveis associados à participação neste estudo:

- Relacionados à coleta de sangue conforme amplamente conhecidos que são extremamente raros;
- Não existe um risco relacionado à ultrassonografia, pois não é um procedimento invasivo e só irá mostrar, caso exista, a presença de nódulos na tireóide.
- Você poderá sentir incômodo com a picada da agulha na PAAF. O risco de infecção é desprezível, pois a PAAF será realizada por profissionais habilitados e com material descartável. É possível que a quantidade de material aspirado de sua tiróide, seja insuficiente para análise; nessa circunstância, será preciso repetir o procedimento.

BENEFÍCIOS

Os benefícios em participar deste estudo são: você será acompanhado para avaliar se apresenta alguma alteração na tireóide, portanto serão realizados os exames de sangue e ultrassonografia, e se necessário, a PAAF.

Caso seus exames apresentem alguma alteração, você será tratado pelos médicos do serviço de Endocrinologia do HUUPD. Este estudo não o reembolsará por sua participação e os gastos com transporte e lanche após coleta de sangue serão financiados, respectivamente, pelo Serviço de Endocrinologia e Nutrição do HUUPD.

TEMPO DE PARTICIPAÇÃO NO ESTUDO

O tempo de participação no estudo terá inicio com a primeira consulta com o médico do projeto e terminará após a avaliação pelo mesmo dos resultados dos exames.

CONFIDENCIALIDADE DO ESTUDO

O registro da participação neste estudo será mantido confidencial. Nós guardaremos os registros de cada indivíduo, em sala trancada, e somente os profissionais trabalhando na equipe terão acesso a estas informações. Cada indivíduo receberá um número para ser utilizado no laboratório. Se qualquer relatório ou publicação resultar deste trabalho, a identificação do paciente não será revelada. Resultados serão relatados de forma RESUMIDA e o indivíduo não será identificado.

PARTICIPAÇÃO VOLUNTÁRIA

Toda participação é voluntária. Não há PUNIÇÃO para alguém que decida não participar neste estudo. Ninguém também será penalizado se decidir desistir de participar do estudo, em qualquer época.

ESCLARECIMENTOS

Estimulamos que você faça perguntas a respeito da pesquisa, sempre que você achar necessário. Se você quiser mais esclarecimentos a respeito da pesquisa ou se surgir alguma dúvida, entre em contato com os integrantes.

Maíra Cristina Carvalho dos Santos

End.: Rua Boa Esperança, 612, Casa 08, condomínio Málaga, Cohama.

Telefone: 81147669/ 32567974

Nome da pessoa (letra de forma):

Responsável

Testemunha

Impressão digital para aqueles que não sabem escrever.

COMPROMISSO DO INVESTIGADOR

Eu discuti as questões acima apresentadas com os indivíduos participantes no estudo. É minha opinião que o indivíduo entende os riscos, benefícios e obrigações relacionadas a este projeto.

São Luis-MA, _____ de _____ de _____.

Assinatura do Pesquisador

8 ARTIGO CIENTÍFICO

8.1 Nome do Periódico

Pituitary.
Editor chefe: Shlomo Melmed.
ISSN: 1386-341X (versão impressa).
ISSN: 1573-7403 (versão online).
Fator de impacto 2010: 2282.

8.2 Normas editoriais/Normas para autores

The Official Journal of the Pituitary Society Editor-in-Chief: Shlomo Melmed

ISSN: 1386-341X (print version) ISSN: 1573-7403 (electronic version)

Journal no. 11102

Instructions for Authors

TYPES OF PAPERS

Pituitary publishes original basic and applied work in the field of hypothalamic-pituitary molecular biology, biochemistry, pathophysiology, clinical diagnosis and management, neurosurgery and radiation therapy. Regular articles, Case Reports, Letters to the Editor as well as solicited and unsolicited reviews are peer-reviewed by the Editor, member of the Editorial Board and ad hoc reviewers.

MANUSCRIPT SUBMISSION

Manuscript Submission

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co- authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been

carried out. The publisher will not be held legally responsible should there be any claims for compensation.

Permissions

Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) for both the print and online format and to include evidence that such permission has been granted when submitting their papers. Any material received without such evidence will be assumed to originate from the authors.

Online Submission

Authors should submit their manuscripts online. Electronic submission substantially reduces the editorial processing and reviewing times and shortens overall publication times. Please follow the hyperlink http://www.springer.com/medicine/internal/journal/11102?print_view=true&detailsPage=pltci_1591207

“Submit online” on the right and upload all of your manuscript files following the instructions given on the screen.

TITLE PAGE

Title Page

The title page should include:

The name(s) of the author(s)

A concise and informative title

The affiliation(s) and address(es) of the author(s)

The e-mail address, telephone and fax numbers of the corresponding author

Abstract

Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

Purpose (stating the main purposes and research question) Methods

Results

Conclusions

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

TEXT

Text Formatting

Manuscripts should be submitted in Word.

Use a normal, plain font (e.g., 10-point Times Roman) for text. Use italics for emphasis.

Use the automatic page numbering function to number the pages. Do not use field functions.

Use tab stops or other commands for indents, not the space bar.

Use the table function, not spreadsheets, to make tables.

Use the equation editor or MathType for equations.

Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Word template (zip, 154 kB)

Manuscripts with mathematical content can also be submitted in LaTeX.

LaTeX macro package (zip, 182 kB)

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section before the reference list. The names of funding organizations should be written in full.

REFERENCES

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples: 1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list.

The entries in the list should be numbered consecutively.

Journal article

Hamburger, C.: Quasimonotonicity, regularity and duality for nonlinear systems of partial differential equations. Ann. Mat. Pura Appl. 169, 321–354 (1995)

Article by DOI

Sajti, C.L., Georgio, S., Khodorkovsky, V., Marine, W.: New nanohybrid materials for biophotonics. Appl. Phys. A (2007). doi:10.1007/s00339-007-4137-z

Book

Geddes, K.O., Czapor, S.R., Labahn, G.: Algorithms for Computer Algebra. Kluwer, Boston (1992)

Book chapter

Broy, M.: Software engineering — from auxiliary to key technologies. In: Broy, M., Denert, E. (eds.) Software Pioneers, pp. 10–13. Springer, Heidelberg (2002)

Online document

Cartwright, J.: Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1 (2007). Accessed 26 June 2007

Always use the standard abbreviation of a journal’s name according to the ISSN List of Title Word Abbreviations, see www.issn.org/2-22661-LTWA-online.php.

For authors using EndNote, Springer provides an output style that supports the formatting of in-text citations and reference list.

EndNote style (zip, 2 kB)

TABLES

All tables are to be numbered using Arabic numerals.

Tables should always be cited in text in consecutive numerical order.

For each table, please supply a table caption (title) explaining the components of the table.

Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.

Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

ARTWORK AND ILLUSTRATIONS GUIDELINES

For the best quality final product, it is highly recommended that you submit all of your artwork – photographs, line drawings, etc. – in an electronic format. Your art will then be produced to the highest standards with the greatest accuracy to detail. The published work will directly reflect the quality of the artwork provided.

Electronic Figure Submission

Supply all figures electronically.

Indicate what graphics program was used to create the artwork.

For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MS Office files are also acceptable.

Vector graphics containing fonts must have the fonts embedded in the files. Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Line Art

Definition: Black and white graphic with no shading.

Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.

All lines should be at least 0.1 mm (0.3 pt) wide.

Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.

Vector graphics containing fonts must have the fonts embedded in the files.

Halftone Art

Definition: Photographs, drawings, or paintings with fine shading, etc.

If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves.

Halftones should have a minimum resolution of 300 dpi.

Combination Art

Definition: a combination of halftone and line art, e.g., halftones containing line drawing,extensive lettering, color diagrams, etc.

Combination artwork should have a minimum resolution of 600 dpi.

Color Art

Color art is free of charge for online publication.

If black and white will be shown in the print version, make sure that the main information will still be visible. Many colors are not distinguishable from one another when converted to black and white. A simple way to check this is to make a xerographic copy to see if the necessary distinctions between the different colors are still apparent.

If the figures will be printed in black and white, do not refer to color in the captions. Color illustrations should be submitted as RGB (8 bits per channel).

Figure Lettering

To add lettering, it is best to use Helvetica or Arial (sans serif fonts).

Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).

Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.

Avoid effects such as shading, outline letters, etc.

Do not include titles or captions within your illustrations.

Figure Numbering

All figures are to be numbered using Arabic numerals.

Figures should always be cited in text in consecutive numerical order. Figure parts should be denoted by lowercase letters (a, b, c, etc.).

If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures, "A1, A2, A3, etc." Figures in online appendices (Electronic Supplementary Material) should, however, be numbered separately.

Figure Captions

Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.

Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.

No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.

Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.

Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

Figure Placement and Size

When preparing your figures, size figures to fit in the column width.

For most journals the figures should be 39 mm, 84 mm, 129 mm, or 174 mm wide and not higher than 234 mm.

For books and book-sized journals, the figures should be 80 mm or 122 mm wide and not higher than 198 mm.

Permissions

If you include figures that have already been published elsewhere, you must obtain permission from the copyright owner(s) for both the print and online format. Please be aware that some publishers do not grant electronic rights for free and that Springer will not be able to refund any costs that may have occurred to receive these permissions. In such cases, material from other sources should be used.

Accessibility

In order to give people of all abilities and disabilities access to the content of your figures, please make sure that

All figures have descriptive captions (blind users could then use a text-to-speech software or a text-to-Braille hardware)

Patterns are used instead of or in addition to colors for conveying information (color-blind users would then be able to distinguish the visual elements)

Any figure lettering has a contrast ratio of at least 4.5:1

ELECTRONIC SUPPLEMENTARY MATERIAL

Springer accepts electronic multimedia files (animations, movies, audio, etc.) and other supplementary files to be published online along with an article or a book chapter. This feature can add dimension to the author's article, as certain information cannot be printed or is more convenient in electronic form.

Submission

Supply all supplementary material in standard file formats.

Please include in each file the following information: article title, journal name, author names; affiliation and e-mail address of the corresponding author.

To accommodate user downloads, please keep in mind that larger-sized files may require very long download times and that some users may experience other problems during downloading.

Audio, Video, and Animations

Always use MPEG-1 (.mpg) format.

Text and Presentations

Submit your material in PDF format; .doc or .ppt files are not suitable for long-term viability. A collection of figures may also be combined in a PDF file.

Spreadsheets

Spreadsheets should be converted to PDF if no interaction with the data is intended.

If the readers should be encouraged to make their own calculations, spreadsheets should be submitted as .xls files (MS Excel).

Specialized Formats

Specialized format such as .pdb (chemical), .wrl (VRML), .nb (Mathematica notebook), and .tex can also be supplied.

Collecting Multiple Files

It is possible to collect multiple files in a .zip or .gz file.

Numbering

If supplying any supplementary material, the text must make specific mention of the material as a citation, similar to that of figures and tables.

Refer to the supplementary files as “Online Resource”, e.g., "... as shown in the animation (Online Resource 3)", “... additional data are given in Online Resource 4”.

Name the files consecutively, e.g. “ESM_3.mpg”, “ESM_4.pdf”.

Captions

For each supplementary material, please supply a concise caption describing the content of the file.

Processing of supplementary files

Electronic supplementary material will be published as received from the author without any conversion, editing, or reformatting.

Accessibility

In order to give people of all abilities and disabilities access to the content of your supplementary files, please make sure that

The manuscript contains a descriptive caption for each supplementary material

Video files do not contain anything that flashes more than three times per second (so that users prone to seizures caused by such effects are not put at risk)

SCIENTIFIC STYLE

Please always use internationally accepted signs and symbols for units (SI units).

Generic names of drugs and pesticides are preferred; if trade names are used, the generic name should be given at first mention.

INTEGRITY OF RESEARCH AND REPORTING

Ethical standards

Manuscripts submitted for publication must contain a declaration that the experiments comply with the current laws of the country in which they were performed. Please include this note in a separate section before the reference list.

Conflict of interest

Authors must indicate whether or not they have a financial relationship with the organization that sponsored the research. This note should be added in a separate section before the reference list.

If no conflict exists, authors should state: The authors declare that they have no conflict of interest.

DOES SPRINGER PROVIDE ENGLISH LANGUAGE SUPPORT?

Manuscripts that are accepted for publication will be checked by our copyeditors for spelling and formal style. This may not be sufficient if English is not your native language and substantial editing would be required. In that case, you may want to have your manuscript edited by a native speaker prior to submission. A clear and concise language will help editors and reviewers concentrate on the scientific content of your paper and thus smooth the peer review process.

The following editing service provides language editing for scientific articles in:

Medicine, biomedical and life sciences, chemistry, physics, engineering, business/economics, and humanities

Edanz Editing Global

Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. Please contact the editing service directly to make arrangements for editing and payment.

AFTER ACCEPTANCE

Upon acceptance of your article you will receive a link to the special Author Query Application at Springer's web page where you can sign the Copyright Transfer Statement online and indicate whether you wish to order OpenChoice and offprints.

Once the Author Query Application has been completed, your article will be processed and you will receive the proofs.

Open Choice

In addition to the normal publication process (whereby an article is submitted to the journal and access to that article is granted to customers who have purchased a subscription), Springer now provides an alternative publishing option: Springer Open Choice. A Springer Open Choice article receives all the benefits of a regular subscription-based article, but in addition is made available publicly through Springer's online platform SpringerLink.

Springer Open Choice

Copyright transfer

Authors will be asked to transfer copyright of the article to the Publisher (or grant the Publisher exclusive publication and dissemination rights). This will ensure the widest possible protection and dissemination of information under copyright laws.

Open Choice articles do not require transfer of copyright as the copyright remains with the author. In opting for open access, the author(s) agree to publish the article under the Creative Commons Attribution License.

Offprints

Offprints can be ordered by the corresponding author.

Color illustrations

Publication of color illustrations is free of charge.

Proof reading

The purpose of the proof is to check for typesetting or conversion errors and the completeness and accuracy of the text, tables and figures. Substantial changes in content, e.g., new results, corrected values, title and authorship, are not allowed without the approval of the Editor.

After online publication, further changes can only be made in the form of an Erratum, which will be hyperlinked to the article.

Online First

The article will be published online after receipt of the corrected proofs. This is the official first publication citable with the DOI. After release of the printed version, the paper can also be cited by issue and page numbers.

8.3 Artigo

Thyroid cancer in patients with acromegaly: A case-control study

Santos, Maíra Cristina Carvalho dos[1]; Nascimento, Gilvan Cortês[1]; Nascimento, Ana Gisélia Cortes[1] ; Carvalho, Viviane Chaves[1] ; Lopes, Maria Honorina Cordeiro[1]; Montenegro, Renan[2]; Montenegro Jr, Renan[2] ; Vilar, Lucio[3] ; Albano, Mônica[2] ; Alves, Alice Regina Vasconcelos[1] ; Parente, Conceição Veiga[1] ; Faria, Manuel dos Santos[1]

1 Endocrinology Unit - Federal University of Maranhão - UFMA ; 2 Endocrinology Unit - Federal University of Ceará - UFC ; 3 Endocrinology Unit - Federal University of Pernambuco - UFPE

Abstract

Several studies have associated acromegaly with an increased risk of benign and malignant tumors. While simple and multinodular goiters are common findings in acromegaly, the prevalence of thyroid cancer is uncertain. The objective of this study was to estimate the prevalence of thyroid cancer in a series of acromegalic patients from three hospitals in northeast of Brazil. The methodology used included morphological, cytological and histological thyroid analysis of acromegalic patients and volunteers over 18 years, matched for age and sex and with nodule (s) ≥ 1 cm. The subjects of this study were 124 acromegalic patients, including 76 females (61.3%) and 48 men (38.7%), with a mean age 45.1 years. Results of the study showed that thyroid ultrasonography was normal in 31 cases (25%), 25 had diffuse goiter (20.1%), 67 had nodules (54%) and one agenesis of the right lobe (0.8%). Thirty six patients underwent fine needle aspiration biopsy (FNAB) of their nodules and 9 cases of papillary cancer were found (7.2%). The control group consisted of 263 subjects, 156 females (59.3%) and 107 males (40.7%), mean age 44.7 years. In ultrasound assessment, 96 had nodules (36.5%). Of these, 13 were punctured and 2 cases of papillary carcinoma were found (0.7%). These results gave an odds ratio of 10.21 (p = 0.0011, 95% CI 2.17 to 48.01). These findings demonstrate an increased prevalence of thyroid cancer, statistically significant when compared to our control group. Thus, it is suggested that acromegalic patients should be routinely submitted to thyroid ultrasound evaluation, followed by FNAB of nodules when indicated.

Keywords: acromegaly and cancer, IGF-1 and cancer, thyroid and acromegaly, GH and cancer

Introduction

Acromegaly is an unusual endocrine disorder characterized by events resulting from sustained hypersecretion of GH and concomitant rise of IGF-1. It is associated with premature mortality caused by cardiovascular, metabolic and respiratory disease, as well as increased risk of certain malignancies [1, 2, 3, 4].

The association between tumor growth and growth hormone (GH), insulin like growth factor-1 axis is well established [5, 6]. However, several reports did not support the increased risk of developing cancer in patients with acromegaly [7, 8].

Conflicting evidence suggests that acromegaly is associated with an increased risk of colonic neoplasia [7, 9, 10]. Mechanisms tought to be involved in the apparent excess risk include a trophic IGF-1 effect on the proliferation of epithelial cells [11], and reduced expression of the peroxisome proliferator-activated receptor (PPAR) gene [12].

In patients with acromegaly there is a high prevalence of goiter, especially non-toxic nodular goiter [13, 14]. Cheung et al found in 37 subjects with acromegaly an overall incidence of 92% of goiter. Their findings suggest that early in the course of the disease, diffuse goiters occurs [15]. However, the increased prevalence of thyroid cancer in these patients remains uncertain.

Part of the difficulty in determining the true incidence of cancer in this population results from the relative rarity of acromegaly. In addition, only after progress is made in treating the disease itself and its complications, are these patients living long enough to reach the age of increased cancer risk [16].

The objective of this study is to determine the prevalence of thyroid cancer in this group of acromegalic patients and to compare the results with a control group.

Materials and methods

Patients

The subjects of this study were 124 acromegalic patients, including 76 females (61.3%) and 48 males (38.7%), with a mean age 45.1 ± 13,4 years. The control group was composed of 263 individuals, of which 156 females (59.3%) and 107 males (40.7%), with a mean age 44.7 ± 13.4 years. Thirty nine subjects from the control group had microadenoma (prolactinoma and nonfunctioning) with normal serum level of GH and IGF-1.

Study protocol and assays

The study was performed in accordance with the declaration of Helsinki and was approved by the local ethics committee. All study participants provided informed consent before enrollment had been reached.

A cross-sectional study including a control group, was performed in the outpatient clinics of the Division of Endocrinology from University Hospital Presidente Dutra - UFMA, University Hospital Walter Cantídio - UFC and Hospital das Clínicas - UFPE (Northeast region of Brazil).

A morphological evaluation (ultrasonography), cytological assessment (puncture of solid and mixed thyroid nodules with size greater than or equal to 1 cm) and histological (when indicated) study of thyroid was performed with a group of patients diagnosed with acromegaly, and volunteers in a control group over 18 years.

Acromegaly was considered with elevated levels of IGF-1 adjusted for sex and age and with GH levels greater than 1 ng/mL after an oral glucose tolerance test with 75g of dextrose plus the identification of pituitary adenoma in MRI scans.

GH and IGF-1 serum levels were measured using the chemiluminescence method (Immulite ® 1000).

Thyroid ultrasound was performed using CO Medison equipment., LTD (KOREA ®), with a 7.5 MHz linear transducer. Thyroid volume was calculated using the De Chiro and Nelson formula for each lobe. Fine needle aspiration biopsy (FNAB) was performed using a 21 G needle connected to a 10 ml disposable syringe without negative pressure, guided by ultrasound. The slides were fixed with alcohol 96 ° or air-dried, and then stained. Hematoxylin-eosin and/or Papanicolaou was used for those fixed with alcohol, and Giemsa stain for air dried slides.

All patients diagnosed with cancer after thyroidectomy had their slides reviewed by two pathologists, and in case of disagreement a third pathologist was called on to assist in the diagnostic conclusion. None of the cancer patients had additional risk factors for differentiated thyroid cancers, besides one submitted to radiotherapy.

Statistics

For comparison of categorical variables, the chi-squared test or the Fisher exact test were used where appropriate. The Student's t test was performed for the comparative analysis of quantitative variables. Results are expressed as percentages and mean values ± SD or unless otherwise indicated. All results were considered significant if P value was less than 0.05.

Results

We evaluated 124 patients with acromegaly, of whom 76 (61.3%) were female and 48 (38.7%) were male, with ages ranging from 18 to 77 years (mean 45.1 ± 13.4 years) (Table 1). In the ultrasound study, 31 (25%) patients had normal thyroid, 25 (20.1%) diffuse goiter, 67 (54%) nodules and one (0.8%) agenesis of the right lobe (Fig.1, table 2). Thirty-six patients (29%) had solid and/ or mixed thyroid nodules with size greater than or equal to 1 cm, all being punctured.

We found 9 (7.25%) cases of cancer, all of them papillary type (3 men and 6 women, mean age of 50.7 ± 10.83 years) (Fig.2, table 2 and 3). In the acromegalic group without cancer (115 patients) the mean age was 44.6 ± 13.5 years, of whom 45 (39.1%) were male and 70 (60.8%) were female (table 2).

Table 1. Demographic characteristics of all participants (n=387).

Variable	Acromegaly group	Control group	P value
Age (Mean ± SD) (years)	45.1 ± 13.4	44.7 ± 13.4	ns*
Male (n/ %)	48 (38.7%)	107 (40.7%)	ns*
Female (n/ %)	76 (61.3%)	156 (59.3%)	ns*
Total	124	263	

* Non significant

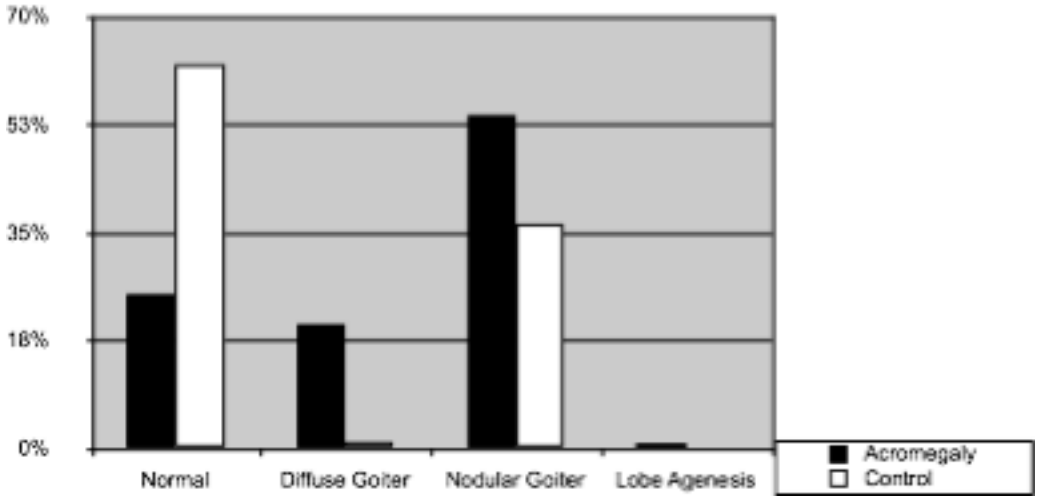

Fig 1. Thyroid ultrasonography findings (n=387)

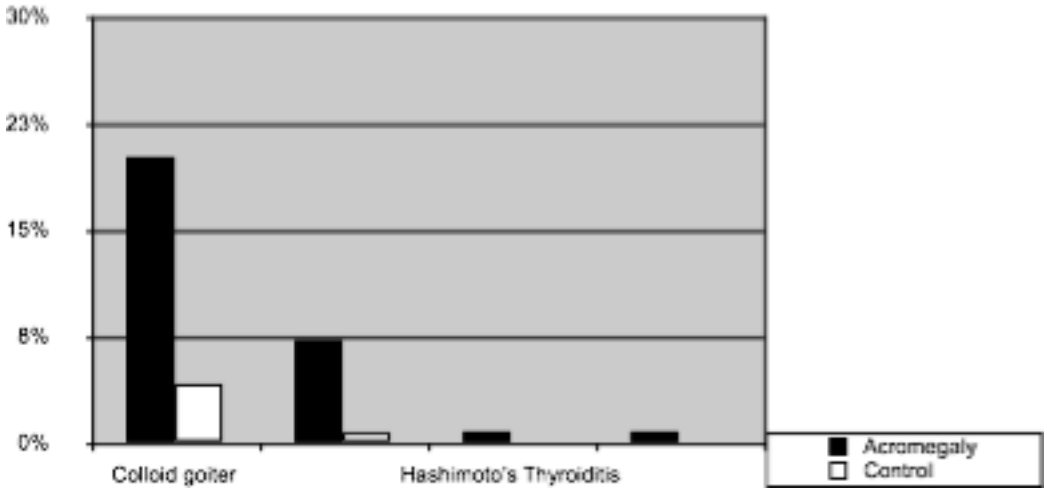

Fig 2 Cytological findings (n=49)

Table 2 . Demographic characteristics and thyroid evaluation in 124 acromegalic patients.

Thyroid morphology (by ultrasound)	
Normal	31 (25%)
Abnormal	93 (75%)
Diffuse goiter	25 (20.1%)
Nodular goiter	67 (54%)
Agenesis of right lobe	1 (0.8%)
FNAB (in nodules > 1cm)	36 (29%)
Benign	26 (20.9%)
Inconclusive	1 (0.8%)
Papillary carcinoma	9 (7.2%)
Acromegalic with thyroid cancer	9 (7.2%)
Age (mean/ years)	50.7*
Male (n/%)	3 (33.3%)*
Female (n/%)	6 (66.7%)*
Acromegalic without thyroid cancer	115 (92.7%)
Age (mean/ years)	44.6*
Male (n/%)	45 (39.1%)*
Female (n/%)	70 (60.8%)*

FNAB: fine needle aspiration biopsy. * non significant

Table 3. Characteristics of Acromegalic patients at the diagnosis of thyroid cancer (n=9)

Patient no.	Age (ys)	Gender	RT	FH	Δt DX (ys)	Pituitary imaging	Histology	Acromegaly status	%IGF-1 ULN
1	62	F	N	N	0	macroadenoma	papillary	uncontrolled	125.6%
2	60	F	N	N	15	macroadenoma	papillary	uncontrolled	117.7%
3	58	F	N	N	4	microadenoma	papillary	controlled for 3 years	< 100%
4	41	M	Y	N	9	macroadenoma	papillary	controlled for 5 years	< 100%
5	56	F	N	N	5	macroadenoma	papillary	uncontrolled	131.5%
6	56	F	N	N	1	macroadenoma	papillary	uncontrolled	111.3%
7	32	M	N	N	5	macroadenoma	papillary	controlled for 1 year	< 100%
8	38	M	N	N	5	macroadenoma	papillary	controlled for 1 year	< 100%
9	54	F	N	N	0	microadenoma	papillary	uncontrolled	N/A

RT: radiotherapy; FH: family history; Δt DX: time from diagnosis of acromegaly; ULN: upper limit of normality; N/A: not available.

The control group consisted of 263 individuals, of whom 156 (59.3%) females and 107 (40.7%) males, aged 19-81 years (mean 44.7 ± 13.4 years) (Table 1). At ultrasonography, 96 (36.5%) control subjects had nodules of varying sizes, while the majority (62.36%) had normal examination (Fig. 1). Thirteen volunteers showed solid and/or mixed thyroid nodules with size greater than or equal to 1 cm, all being punctured, and two cases of papillary carcinoma found (0.7%) (Fig.2).

These results gave an odds ratio of 10.21 (P = 0.0011, 95% CI 2.17 - 48.01) for thyroid cancer in patients with acromegaly (Table 4).

Table 4. Prevalence of thyroid carcinoma in the sample (n=387)

Variable	Acromegaly group	Control group	Odds Ratio
Case (n)	9 (7.2%)	2 (0.7%)	10.21(CI 2.17-48.01)*
Age (Mean/ years)	50.7	39.5	
Male (n/ %)	3 (33.3%)	1 (50%)	
Female (n/ %)	6 (66.7%)	1 (50%)	

* p value= 0.0011

Discussion

Over the last decade, several epidemiological studies and laboratory experiments have linked the IGF system with neoplasia [1,17]. Population studies show a slight increase in the risk of subsequent diagnosis of cancer in people with IGF-1 levels in the upper limit of normal compared to those whose values were the lower limit of normal [17]. Multiple signaling pathways are activated after interaction between the IGF-1 receptor and its ligands. After activation, these signaling pathways can stimulate multiple neoplastic phenotypes including proliferation, protection from apoptosis, invasion and metastasis [18].

As far as thyroid is concerned, there seems to be an association between acromegaly and thyroid goiter and its prevalence varies from 11 to 92% depending on the method used, whether palpation or ultrasound [15, 19, 20]. Our series of 124 patients with acromegaly showed a prevalence of thyroid changes around 74%, including nodular (54%) and diffuse goiters (20.1%), while in the control group this was respectively 36.5% and 1.1%. This is in agreement with Gasperi et al who analyzed 258 patients with acromegaly, of whom 78% had an alteration in thyroid, particularly non-toxic nodular goiter [13], and Tita et al who demonstrated a prevalence of diffuse and nodular goiter which totaled 82% of the group [21]. As TSH and IGF-1 are known to act synergistically on thyroid cell growth *in vitro*, the mechanism of thyroid growth in acromegalic patients has generally been attributed to the elevated IGF-1 levels [21].

The prevalence of thyroid cancer in acromegaly is not known, as the populations of acromegalic patients studied are too small. Epidemiological studies have reported an increased risk of cancer in acromegalic patients when compared to the general population [8, 22]. Tita et al estimated the prevalence of thyroid cancer at 5.6% (7/125) in acromegalic patients, as compared to 0.1% in the general population over iodine deficient areas [21]. In an Italian multicenter study, a thyroid cancer prevalence of 1.2% (3/258 patients) was found by Gasperi et al [13], while in the study of Kurimoto et al the percentage was 4.8% [23] and recent data from Gullu et al showed that thyroid cancer is the most common cancer associated with acromegaly (4.7%) [24]. Supporting this, Vannelli et al demonstrated production of IGF-1 in cultured human thyroid cells, as well as the presence of its receptor. They confirmed these findings in normal cells and neoplastic cells, and in the latter the concentration

of IGF-1 was higher, suggesting that IGF-1 may contribute to the abnormal growth of tumors [25]. We also know that, the vast majority of malignant neoplasms derived from epithelial cells express genes encoding the IGF-1 receptor (IGF-1R) leading to anti-apoptotic and mitogenic activity, angiogenesis, lymphangiogenesis and cell motility when activated (6, 26, 27). It is also possible that hyperinsulinism indirectly promotes carcinogenesis through reduction of hepatic IGFBP-1 and possibly IGFBP-2, resulting in increased circulating levels of free and bioactive IGF-1 [28, 29, 30]. These results suggest that the augmented systemic GH/IGF-I axis due to acromegaly and the local expression of GH/IGF-I components in the tumor tissues may be involved in the process of oncogenesis and/or growth.

We found nine cases of thyroid cancer in the group with acromegaly, and just one had undergone radiotherapy for adenoma's treatment with 37 years old. In this particular case the diagnosis of thyroid cancer occurred after 7 years of radiotherapy. None had family history of thyroid cancer. There is an increased risk of second intracranial tumour in patients with pituitary adenoma treated with radiotherapy. The reported tumors include astrocytoma, glioblastoma, meningioma, and sarcoma. There was no evidence of excess risk of thyroid malignancy [31, 32, 33, 34]. The mean age of this group was 50.7 years old, with a higher proportion of women (66%). In all cases, the nodules were solid, hypoechoic, without associated lymphadenopathy and four had calcifications. Noteworthy that four patients had biochemically controlled acromegaly and five did not.

Our control group was selected on demand (n=263), matched for age and sex, in which we found a prevalence of thyroid cancer at a rate of 0.7% (2/263), consisting of one woman and one man, mean age was 39.5 years old, with no family history of thyroid cancer or radiotherapy, with ultrasound showing in one case a mixed nodule and in the other, hypoechoic nodule with lymphadenopaty; while the acromegalic group rate was 7.25% (9/124) with an odds ratio of 10.21 ($P = 0.0011$, 95% CI 2.17 - 48.01). All patients with thyroid cancer were of papillary type.

In an attempt to minimize biases, as an increased thyroid cancer rate in acromegalic subjects might also be attributed only to increased surveillance, all acromegalic patients and the control group were from the same region of the country (northeast) and were submitted to the same evaluation criteria. We highlight that our findings are strikingly high when compared to our control group that was well matched, as well as the records of thyroid cancer in Recife (northeast of Brazil)

show an incidence rate of 1.2 and 3.5/100000 respectively for man and woman and point to a lower incidence in this city when compared to other regions of Brazil [35]. In addition, 39 individuals from the control group had microadenoma, with normal serum level of GH and IGF-1, where we found 14 (35.9%) with nodular goiters and no thyroid carcinoma. This finding may support the hypothesis that the observation of increased thyroid cancer rate is specifically linked to acromegaly, as pointed out by Tita et al [21].

We did not find statistically significant differences in age and sex of acromegalic patients with and without thyroid cancer. However, due to the small patient and event numbers, it is difficult to adjust for such major confounding factors. Moreover the length of exposure to GH excess is unknown, as the symptoms of acromegaly can be insidious, with diagnosis lagging behind onset, and definitive biochemical remission does not reliably follow treatment [36]. Additionally, we should stress that in our study we investigated only thyroid nodules greater than or equal to one centimeter, while the current guidelines recommend puncturing all nodules with suspicious ultrasonographic aspects, regardless of size. Therefore, our number of patients with a diagnosis of thyroid cancer could actually be even higher.

In general differentiated thyroid cancer presents a good prognosis, with statistics from around the world showing the decline in mortality. However in the acromegalic population it is necessary to verify whether or not these tumors present a more aggressive behavior, a greater frequency of BRAF mutations and to determine if survival curves are different from those known for differentiated thyroid carcinomas. Moreover, it is important to take into consideration that the genetic susceptibility to GH-producing pituitary tumors could also predispose the patient to the development of other tumors, and epigenetic mechanisms could also contribute to this increased risk [6, 18, 37].

In conclusion, our findings show a statistically significant increased prevalence of thyroid cancer in acromegalic patients when compared to a control group. Thus, our data suggest that acromegalic patients should be routinely screened by thyroid ultrasound, followed by FNAB, particularly, in cases of nodules ≥ 1 cm.

References

1. Clayton PE, Banerjee I, Murray PG, Renehan AG.: Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. Nat Rev Endocrinol 7, 11-24 (2011)
2. Melmed S.: Medical progress: acromegaly. N Engl J Med 355, 2558–2573 (2006)
3. Colao A, Ferone D, Marzullo P, Lombardi G.: Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev 25, 102-152 (2004)
4. Melmed S et al.: Guidelines for Acromegaly Management: An Update. J Clin Endocrinol Metab 94, 1509-17 (2009)
5. Cohen P, Clemmons DR, Rosenfeld RG.: Does the GH-IGF-1 axis play a role in cancer pathogenesis? Growth Horm IGF Res 10, 297-305 (2000)
6. Renehan AG, Brennan BM.: Acromegaly, growth hormone and cancer risk. Best Pract Res Clin Endocrinol Metab 22, 639-57 (2008)
7. Melmed S.: Acromegaly and cancer: not a problem? J Clin Endocrinol Metab 86, 2929-2934 (2001)
8. Orme SM, McNally RJ, Cartwright RA, Belchetz PE.: Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab 83, 2730-4 (1998)
9. Terzolo et al.: Colonoscopic screening and follow-up inpatients with acromegaly: a multicenter study in Italy. J Clin Endocrinol Metab 90, 84-90 (2005)
10. Rokkas T et al.: Risk of colorectal neoplasm in patients with acromegaly: a meta-analysis. World J Gastroenterol 14: 3484–3489 (2008)
11. Cats A et al.: Increased epithelial cell proliferation in the colon of patients with acromegaly. Cancer Res 56, 523-6 (1996)
12. Bogazzi F et al.: Changes in the expression of the peroxisome proliferator-activated receptor gamma gene in the colonic polyps and colonic mucosa of acromegalic patients. J Clin Endocrinol Metab 88, 3938-42 (2003)
13. Gasperi M, Martino E, Manetti L, Arosio M, Porretti S, Faglia G, et al.: Prevalence of thyroid diseases in patients with acromegaly: results of an Italian multicenter study. J Endocrinol Invest 25, 240-245 (2002)
14. Ruchala M, Skiba A, Gurgul E et al.: The occurrence of thyroid focal lesions and a need for fine needle aspiration biopsy in patients with acromegaly due to an increased risk of thyroid cancer. Neuro Endocrinol Lett 30, 382-386 (2009)
15. Cheung NW, Boyages SC.: The thyroid gland in acromegaly: an ultrasonographic study. Clin Endocrinol (Oxf) 46, 545-9 (1997)
16. Jenkins PJ, Besser M.: Clinical perspective: acromegaly and cancer: a problem. J Clin Endocrinol Metab 86, 2935-41 (2001)
17. Pollak M.: Insulin, insulin-like growth factors and neoplasia. Best Pract Res Clin Endocrinol Metab 22, 625-38 (2008)
18. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D.: Diabetes and cancer: a consensus report. CA Cancer J Clin 60, 207-21 (2010)
19. Loeper S, Ezzat S.: Acromegaly: re-thinking the cancer risk. Rev Endocr Metab Disord 9, 41-58 (2008)
20. Kasagi K et al.: Goiter associated with acromegaly: sonographic and scintigraphic findings of the thyroid gland. Thyroid 9, 791-796 (1999)
21.Tita P et al.: High prevalence of differentiated thyroid carcinoma in acromegaly. Clin Endocrinol (Oxf) 63, 161-7 (2005)
22. Baris D et al.: Acromegaly and cancer risk: a cohort study in Sweden and Denmark. Cancer Causes Control 13, 395-400 (2002)
23. Kurimoto M et al.: The prevalence of benign and malignant tumors in patient with acromegaly at a single institute. Endocr J 55, 67-71 (2008)
24. Gullu BE et al.: Thyroid cancer is the most common cancer associated with acromegaly. Pituitary 13, 242-8 (2010)
25. Vannelli GB et al.: Insulin-like growth factor-I receptors in nonfunctioning thyroid nodules. J Clin Endocrinol Metab 71, 1175-82 (1990)
26. Manousos O et al.: IGF-I and IGF-II in relation to colorectal cancer. International Journal of Cancer 83, 15-17 (1999)
27. Jenkins PJ et al.: Insulin-like growth factor I and the development of colorectal neoplasia in acromegaly. J Clin Endocrinol Metab 85, 3218-3221 (2000)
28. Suikkari AM et al.: Insulin regulates the serum levels of low molecular weight insulin-like growth factor-binding protein. J Clin Endocrinol Metab 66, 266-72 (1988)

29. Böni-Schnetzler M.: Insulin regulates the expression of the insulin-like growth factor binding protein 2 mRNA in rat hepatocytes. Mol Endocrinol 4, 1320-6 (1990)
30. Giovannucci E.: Insulin and colon cancer. Cancer Causes Control 6, 164-179 (1995)
31. Brada M et al.: Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. BMJ 304, 1343-1346 (1992)
32. Tsang RW et al.: Glioma arising after radiation therapy for pituitary adenoma. A report of four patients and estimation of risk. Cancer 72, 2227 (1993)
33. Minniti G et al.: Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. J Clin Endocrinol Metab 90, 800-804 (2005)
34. Ayuk J & Stewart PM: Mortality following pituitary radiotherapy. Pituitary 12, 35-39 (2009)
35. Coeli CM et al.: Incidência e mortalidade por câncer de tireóide no Brasil. Arq Bras Endocrinol Metab 49, 503-509 (2005)
36. Wexler TL et al.: Growth hormone status predicts left ventricular mass in patients after cure of acromegaly. Growth Hormone and IGF Research 20, 333-337 (2010)

Pituitary
DOI 10.1007/s11102-012-0383-y

Thyroid cancer in patients with acromegaly: a case–control study

Maíra Cristina Carvalho dos Santos · Gilvan Cortês Nascimento · Ana Gisélia Cortês Nascimento · Viviane Chaves Carvalho · Maria Honorina Cordeiro Lopes · Renan Montenegro · Renan Montenegro Jr. · Lucio Vilar · Mônica Fiterman Albano · Alice Regina Vasconcelos Alves · Conceição Veiga Parente · Manuel dos Santos Faria

Abstract Several studies have associated acromegaly with an increased risk of benign and malignant tumors. While simple and multinodular goiters are common findings in acromegaly, the prevalence of thyroid cancer is uncertain. The objective of this study was to estimate the prevalence of thyroid cancer in a series of acromegalic patients from three hospitals in northeast of Brazil. The methodology used included morphological, cytological and histological thyroid analysis of acromegalic patients and volunteers over 18 years, matched for age and sex and with nodule (s) ≥1 cm. The subjects of this study were 124 acromegalic patients, including 76 females (61.3%) and 48 men (38.7%), with a mean age 45.1 years. Results of the study showed that thyroid ultrasonography was normal in 31 cases (25%), 25 had diffuse goiter (20.1%), 67 had nodules (54%) and one agenesis of the right lobe (0.8%). Thirty-six patients underwent fine needle aspiration biopsy (FNAB) of their nodules and 9 cases of papillary cancer were found (7.2%). The control group consisted of 263 subjects, 156 females (59.3%) and 107 males (40.7%), mean age 44.7 years. In ultrasound assessment, 96 had nodules (36.5%). Of these, 13 were punctured and 2 cases of papillary carcinoma were found (0.7%). These results gave an odds ratio of 10.21 ($p = 0.0011$, 95% CI 2.17 to 48.01). These findings demonstrate an increased prevalence of thyroid cancer, statistically significant when compared to our control group. Thus, it is suggested that acromegalic patients should be routinely submitted to thyroid ultrasound evaluation, followed by FNAB of nodules when indicated.

Keywords Acromegaly and cancer · IGF-1 and cancer · Thyroid and acromegaly · GH and cancer

M. C. C. dos Santos · G. C. Nascimento · A. G. C. Nascimento · M. H. C. Lopes · A. R. V. Alves · C. V. Parente · M. dos Santos Faria (✉)
Endocrinology Unit, Federal University of Maranhão (UFMA), Maranhão, Brazil
e-mail: mfaria@inlabmail.com

V. C. Carvalho
Pathology Unit, Federal University of Maranhão (UFMA), Maranhão, Brazil

R. Montenegro · R. Montenegro Jr. · M. F. Albano
Endocrinology Unit, Federal University of Ceará (UFC), Ceará, Brazil

L. Vilar
Endocrinology Unit, Federal University of Pernambuco (UFPE), Pernambuco, Brazil

Introduction

Acromegaly is an unusual endocrine disorder characterized by events resulting from sustained hypersecretion of GH and concomitant rise of IGF-1. It is associated with premature mortality caused by cardiovascular, metabolic and respiratory disease, as well as increased risk of certain malignancies [1–4].

The association between tumor growth and growth hormone (GH), insulin like growth factor-1 axis is well established [5, 6]. However, several reports did not support the increased risk of developing cancer in patients with acromegaly [7, 8].

Conflicting evidence suggests that acromegaly is associated with an increased risk of colonic neoplasia [7, 9, 10]. Mechanisms tought to be involved in the apparent excess risk include a trophic IGF-1 effect on the proliferation of epithelial cells [11], and reduced expression of the peroxisome proliferator-activated receptor (PPAR) gene [12].

Published online: 21 April 2012

In patients with acromegaly there is a high prevalence of goiter, especially non-toxic nodular goiter [13, 14]. Cheung et al. [15] found in 37 subjects with acromegaly an overall incidence of 92% of goiter. Their findings suggest that early in the course of the disease, diffuse goiters occurs. However, the increased prevalence of thyroid cancer in these patients remains uncertain.

Part of the difficulty in determining the true incidence of cancer in this population results from the relative rarity of acromegaly. In addition, only after progress is made in treating the disease itself and its complications, are these patients living long enough to reach the age of increased cancer risk [16].

The objective of this study is to determine the prevalence of thyroid cancer in this group of acromegalic patients and to compare the results with a control group.

Materials and methods

Patients

The subjects of this study were 124 acromegalic patients, including 76 females (61.3%) and 48 males (38.7%), with a mean age 45.1 ± 13,4 years. The control group was composed of 263 individuals, of which 156 females (59.3%) and 107 males (40.7%), with a mean age 44.7 ± 13.4 years. Thirty-nine subjects from the control group had microadenoma (prolactinoma and nonfunctioning) with normal serum level of GH and IGF-1.

Study protocol and assays

The study was performed in accordance with the declaration of Helsinki and was approved by the local ethics committee. All study participants provided informed consent before enrollment had been reached.

A cross-sectional study including a control group, was performed in the outpatient clinics of the Division of Endocrinology from University Hospital Presidente Dutra—UFMA, University Hospital Walter Cantídio—UFC and Hospital das Clínicas—UFPE (Northeast region of Brazil).

A morphological evaluation (ultrasonography), cytological assessment (puncture of solid and mixed thyroid nodules with size ≥1 cm) and histological (when indicated) study of thyroid was performed with a group of patients diagnosed with acromegaly, and volunteers in a control group over 18 years.

Acromegaly was considered with elevated levels of IGF-1 adjusted for sex and age and with GH levels greater than 1 ng/mL after an oral glucose tolerance test with 75 g of dextrose plus the identification of pituitary adenoma in MRI scans.

GH and IGF-1 serum levels were measured using the chemiluminescence method (Immulite® 1000).

Thyroid ultrasound was performed using CO Medison equipment., LTD (KOREA®), with a 7.5 MHz linear transducer. Thyroid volume was calculated using the De Chiro and Nelson formula for each lobe. Fine needle aspiration biopsy (FNAB) was performed using a 21 G needle connected to a 10 ml disposable syringe without negative pressure, guided by ultrasound. The slides were fixed with alcohol 96° or air-dried, and then stained. Hematoxylin-eosin and/or Papanicolaou was used for those fixed with alcohol, and Giemsa stain for air dried slides.

All patients diagnosed with cancer after thyroidectomy had their slides reviewed by two pathologists, and in case of disagreement a third pathologist was called on to assist in the diagnostic conclusion. None of the cancer patients had additional risk factors for differentiated thyroid cancers, besides one submitted to radiotherapy.

Statistics

For comparison of categorical variables, the Chi-squared test or the Fisher exact test were used where appropriate. The Student's *t* test was performed for the comparative analysis of quantitative variables. Results are expressed as percentages and mean values ± SD or unless otherwise indicated. All results were considered significant if *P* value was less than 0.05.

Results

We evaluated 124 patients with acromegaly, of whom 76 (61.3%) were female and 48 (38.7%) were male, with ages ranging from 18 to 77 years (mean 45.1 ± 13.4 years) (Table 1). In the ultrasound study, 31 (25%) patients had normal thyroid, 25 (20.1%) diffuse goiter, 67 (54%) nodules and one (0.8%) agenesis of the right lobe (Fig. 1; Table 2). Thirty-six patients (29%) had solid and/or mixed thyroid nodules with size greater than or equal to 1 cm, all being punctured.

We found 9 (7.25%) cases of cancer, all of them papillary type (3 men and 6 women, mean age of 50.7 ± 10.83 years) (Fig. 2; Tables 2 and 3). In the acromegalic

Table 1 Demographic characteristics of all participants ($n = 387$)

Variable	Acromegaly group	Control group	*P* value
Age (mean ± SD) (years)	45.1 ± 13.4	44.7 ± 13.4	ns*
Male (n/%)	48 (38.7%)	107 (40.7%)	ns*
Female (n/%)	76 (61.3%)	156 (59.3%)	ns*
Total	124	263	

* Non significant

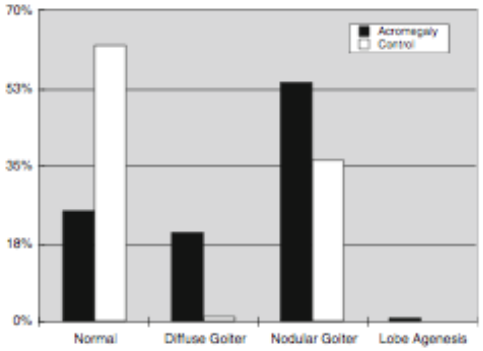

Fig. 1 Thyroid ultrasonography findings ($n = 387$)

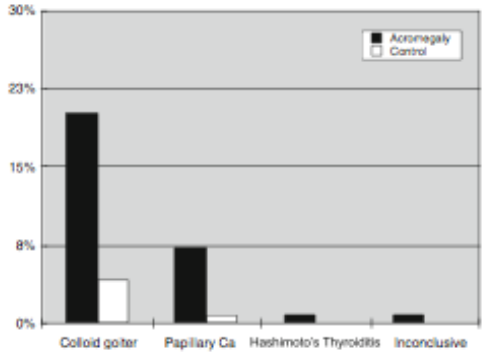

Fig. 2 Cytological findings ($n = 49$)

Table 2 Demographic characteristics and thyroid evaluation in 124 acromegalic patients

Thyroid morphology (by ultrasound)	
Normal	31 (25%)
Abnormal	93 (75%)
Diffuse goiter	25 (20.1%)
Nodular goiter	67 (54%)
Agenesis of right lobe	1 (0.8%)
FNAB (in nodules >1 cm)	36 (29%)
Benign	26 (20.9%)
Inconclusive	1 (0.8%)
Papillary carcinoma	9 (7.2%)
Acromegalic with thyroid cancer	9 (7.2%)
Age (mean/years)	50.7*
Male (*n*/%)	3 (33.3%)*
Female (*n*/%)	6 (66.7%)*
Acromegalic without thyroid cancer	115 (92.7%)
Age (mean/years)	44.6*
Male (*n*/%)	45 (39.1%)*
Female (*n*/%)	70 (60.8%)*

FNAB fine needle aspiration biopsy

* Non significant

group without cancer (115 patients) the mean age was 44.6 ± 13.5 years, of whom 45 (39.1%) were male and 70 (60.8%) were male (Table 2).

The control group consisted of 263 individuals, of whom 156 (59.3%) females and 107 (40.7%) males, aged 19–81 years (mean 44.7 ± 13.4 years) (Table 1). At ultrasonography, 96 (36.5%) control subjects had nodules of varying sizes, while the majority (62.36%) had normal examination (Fig. 1). Thirteen volunteers showed solid and/or mixed thyroid nodules with size greater than or equal to 1 cm, all being punctured, and two cases of papillary carcinoma found (0.7%) (Fig. 2).

These results gave an odds ratio of 10.21 ($P = 0.0011$, 95% CI 2.17–48.01) for thyroid cancer in patients with acromegaly (Table 4).

Discussion

Over the last decade, several epidemiological studies and laboratory experiments have linked the IGF system with neoplasia [1, 17]. Population studies show a slight increase in the risk of subsequent diagnosis of cancer in people with IGF-1 levels in the upper limit of normal compared to those whose values were the lower limit of normal [17]. Multiple signaling pathways are activated after interaction between the IGF-1 receptor and its ligands. After activation, these signaling pathways can stimulate multiple neoplastic phenotypes including proliferation, protection from apoptosis, invasion and metastasis [18].

As far as thyroid is concerned, there seems to be an association between acromegaly and thyroid goiter and its prevalence varies from 11 to 92% depending on the method used, whether palpation or ultrasound [15, 19, 20]. Our series of 124 patients with acromegaly showed a prevalence of thyroid changes around 74%, including nodular (54%) and diffuse goiters (20.1%), while in the control group this was respectively 36.5 and 1.1%. This is in agreement with Gasperi et al. [13] who analyzed 258 patients with acromegaly, of whom 78% had an alteration in thyroid, particularly non-toxic nodular goiter, and Tita et al. [21] who demonstrated a prevalence of diffuse and nodular goiter which totaled 82% of the group. As TSH and IGF-1 are known to act synergistically on thyroid cell growth in vitro, the mechanism of thyroid growth in acromegalic patients has generally been attributed to the elevated IGF-1 levels [21].

The prevalence of thyroid cancer in acromegaly is not known, as the populations of acromegalic patients studied

Table 3 Characteristics of acromegalic patients at the diagnosis of thyroid cancer ($n = 9$)

Patient no.	Age (years)	Gender	RT	FH	Δt DX (years)	Pituitary imaging	Histology	Acromegaly status	%IGF-1 ULN
1	62	F	N	N	0	Macroadenoma	Papillary	Uncontrolled	125.6%
2	60	F	N	N	15	Macroadenoma	Papillary	Uncontrolled	117.7%
3	58	F	N	N	4	Microadenoma	Papillary	Controlled for 3 years	<100%
4	41	M	Y	N	9	Macroadenoma	Papillary	Controlled for 5 years	<100%
5	56	F	N	N	5	Macroadenoma	Papillary	Uncontrolled	131.5%
6	56	F	N	N	1	Macroadenoma	Papillary	Uncontrolled	111.3%
7	32	M	N	N	5	Macroadenoma	Papillary	Controlled for 1 year	<100%
8	38	M	N	N	5	Macroadenoma	Papillary	Controlled for 1 year	<100%
9	54	F	N	N	0	Microadenoma	Papillary	Uncontrolled	N/A

RT radiotherapy, *FH* family history, *Δt DX* time from diagnosis of acromegaly, *ULN* upper limit of normality, *N/A* not available

Table 4 Prevalence of thyroid carcinoma in the sample ($n = 387$)

Variable	Acromegaly group	Control group	Odds ratio
Case (*n*)	9 (7.2%)	2 (0.7%)	10.21(CI 2.17–48.01)*
Age (mean/years)	50.7	39.5	
Male (*n*/%)	3 (33.3%)	1 (50%)	
Female (*n*/%)	6 (66.7%)	1 (50%)	

* p value = 0.0011

are too small. Epidemiological studies have reported an increased risk of cancer in acromegalic patients when compared to the general population [8, 22]. Tita et al. [21] estimated the prevalence of thyroid cancer at 5.6% (7/125) in acromegalic patients, as compared to 0.1% in the general population over iodine deficient areas. In an Italian multicenter study, a thyroid cancer prevalence of 1.2% (3/258 patients) was found by Gasperi et al. [13], while in the study of Kurimoto et al. [23] the percentage was 4.8% and recent data from Gullu et al. [24] showed that thyroid cancer is the most common cancer associated with acromegaly (4.7%). Supporting this, Vannelli et al. [25] demonstrated production of IGF-1 in cultured human thyroid cells, as well as the presence of its receptor. They confirmed these findings in normal cells and neoplastic cells, and in the latter the concentration of IGF-1 was higher, suggesting that IGF-1 may contribute to the abnormal growth of tumors. We also know that, the vast majority of malignant neoplasms derived from epithelial cells express genes encoding the IGF-1 receptor (IGF-1R) leading to anti-apoptotic and mitogenic activity, angiogenesis, lymphangiogenesis and cell motility when activated [6, 26, 27]. It is also possible that hyperinsulinism indirectly promotes carcinogenesis through reduction of hepatic IGFBP-1 and possibly IGFBP-2, resulting in increased circulating levels of free and bioactive IGF-1 [28–30]. These results suggest that the augmented systemic GH/IGF-I axis due to acromegaly and the local expression of GH/IGF-I components in the tumor tissues may be involved in the process of oncogenesis and/or growth.

We found nine cases of thyroid cancer in the group with acromegaly, and just one had undergone radiotherapy for adenoma's treatment with 37 years old. In this particular case the diagnosis of thyroid cancer occurred after 7 years of radiotherapy. None had family history of thyroid cancer. There is an increased risk of second intracranial tumour in patients with pituitary adenoma treated with radiotherapy. The reported tumors include astrocytoma, glioblastoma, meningioma, and sarcoma. There was no evidence of excess risk of thyroid malignancy [31–34]. The mean age of this group was 50.7 years old, with a higher proportion of women (66%). In all cases, the nodules were solid, hypoechoic, without associated lymphadenopathy and four had calcifications. Noteworthy that four patients had biochemically controlled acromegaly and five did not.

Our control group was selected on demand ($n = 263$), matched for age and sex, in which we found a prevalence of thyroid cancer at a rate of 0.7% (2/263), consisting of one woman and one man, mean age was 39.5 years old, with no family history of thyroid cancer or radiotherapy, with ultrasound showing in one case a mixed nodule and in the other, hypoechoic nodule with lymphadenopaty; while the acromegalic group rate was 7.25% (9/124) with an odds ratio of 10.21 ($P = 0.0011$, 95% CI 2.17–48.01). All patients with thyroid cancer were of papillary type.

In an attempt to minimize biases, as an increased thyroid cancer rate in acromegalic subjects might also be attributed only to increased surveillance, all acromegalic patients and the control group were from the same region of the country (northeast) and were submitted to the same evaluation criteria. We highlight that our findings are strikingly high when compared to our control group that was well matched, as well as the records of thyroid cancer in Recife (northeast of Brazil) show an incidence rate of 1.2 and 3.5/100,000, respectively for man and woman and point to a

lower incidence in this city when compared to other regions of Brazil [35]. In addition, 39 individuals from the control group had microadenoma, with normal serum level of GH and IGF-1, where we found 14 (35.9%) with nodular goiters and no thyroid carcinoma. This finding may support the hypothesis that the observation of increased thyroid cancer rate is specifically linked to acromegaly, as pointed out by Tita et al. [21].

We did not find statistically significant differences in age and sex of acromegalic patients with and without thyroid cancer. However, due to the small patient and event numbers, it is difficult to adjust for such major confounding factors. Moreover, the length of exposure to GH excess is unknown, as the symptoms of acromegaly can be insidious, with diagnosis lagging behind onset, and definitive biochemical remission does not reliably follow treatment [36]. Additionally, we should stress that in our study we investigated only thyroid nodules greater than or equal to one centimeter, while the current guidelines recommend puncturing all nodules with suspicious ultrasonographic aspects, regardless of size. Therefore, our number of patients with a diagnosis of thyroid cancer could actually be even higher.

In general differentiated thyroid cancer presents a good prognosis, with statistics from around the world showing the decline in mortality. However, in the acromegalic population it is necessary to verify whether or not these tumors present a more aggressive behavior, a greater frequency of BRAF mutations and to determine if survival curves are different from those known for differentiated thyroid carcinomas. Moreover, it is important to take into consideration that the genetic susceptibility to GH-producing pituitary tumors could also predispose the patient to the development of other tumors, and epigenetic mechanisms could also contribute to this increased risk [6, 18, 19].

In conclusion, our findings show a statistically significant increased prevalence of thyroid cancer in acromegalic patients when compared to a control group. Thus, our data suggest that acromegalic patients should be routinely screened by thyroid ultrasound, followed by FNAB, particularly, in cases of nodules ≥1 cm.

References

1. Clayton PE, Banerjee I, Murray PG, Renehan AG (2011) Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. Nat Rev Endocrinol 7:11–24
2. Melmed S (2006) Medical progress: acromegaly. N Engl J Med 355:2558–2573
3. Colao A, Ferone D, Marzullo P, Lombardi G (2004) Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev 25:102–152
4. Melmed S, Colao A, Barkan A et al (2009) Guidelines for acromegaly management: an update. J Clin Endocrinol Metab 94:1509–1517
5. Cohen P, Clemmons DR, Rosenfeld RG et al (2000) Does the GH-IGF-1 axis play a role in cancer pathogenesis? Growth Horm IGF Res 10: 297–305
6. Renehan AG, Brennan BM (2008) Acromegaly, growth hormone and cancer risk. Best Pract Res Clin Endocrinol Metab 22:639–657
7. Melmed S (2001) Acromegaly and cancer: not a problem? J Clin Endocrinol Metab 86:2929–2934
8. Orme SM, McNally RJ, Cartwright RA, Belchetz PE (1998) Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom acromegaly study group. J Clin Endocrinol Metab 83:2730–2734
9. Terzolo M, Reimondo G, Gasperi M et al (2005) Colonoscopic screening and follow-up inpatients with acromegaly: a multicenter study in Italy. J Clin Endocrinol Metab 90:84–90
10. Rokkas T et al (2008) Risk of colorectal neoplasm in patients with acromegaly: a meta-analysis. World J Gastroenterol 14:3484–3489
11. Cats A et al (1996) Increased epithelial cell proliferation in the colon of patients with acromegaly. Cancer Res 56:523–526
12. Bogazzi F et al (2003) Changes in the expression of the peroxisome proliferator-activated receptor gamma gene in the colonic polyps and colonic mucosa of acromegalic patients. J Clin Endocrinol Metab 88:3938–3942
13. Gasperi M, Martino E, Manetti L, Arosio M, Porretti S, Faglia G et al (2002) Prevalence of thyroid diseases in patients with acromegaly: results of an Italian multicenter study. J Endocrinol Invest 25:240–245
14. Ruchala M, Skiba A, Gurgul E et al (2009) The occurrence of thyroid focal lesions and a need for fine needle aspiration biopsy in patients with acromegaly due to an increased risk of thyroid cancer. Neuro Endocrinol Lett 30:382–386
15. Cheung NW, Boyages SC (1997) The thyroid gland in acromegaly: an ultrasonographic study. Clin Endocrinol (Oxf) 46:545–549
16. Jenkins PJ, Besser M (2001) Clinical perspective: acromegaly and cancer: a problem. J Clin Endocrinol Metab 86:2935–2941
17. Pollak M (2008) Insulin, insulin-like growth factors and neoplasia. Best Pract Res Clin Endocrinol Metab 22:625–638
18. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D (2010) Diabetes and cancer: a consensus report. CA Cancer J Clin 60:207–221
19. Loeper S, Ezzat S (2008) Acromegaly: re-thinking the cancer risk. Rev Endocr Metab Disord 9:41–58
20. Kasagi K et al (1999) Goiter associated with acromegaly: sonographic and scintigraphic findings of the thyroid gland. Thyroid 9:791–796
21. Tita P et al (2005) High prevalence of differentiated thyroid carcinoma in acromegaly. Clin Endocrinol (Oxf) 63:161–167
22. Baris D et al (2002) Acromegaly and cancer risk: a cohort study in Sweden and Denmark. Cancer Causes Control 13:395–400
23. Kurimoto M et al (2008) The prevalence of benign and malignant tumors in patient with acromegaly at a single institute. Endocr J 55:67–71
24. Gullu BE et al (2010) Thyroid cancer is the most common cancer associated with acromegaly. Pituitary 13:242–248
25. Vannelli GB et al (1990) Insulin-like growth factor-I receptors in nonfunctioning thyroid nodules. J Clin Endocrinol Metab 71:1175–1182
26. Manousos O et al (1999) IGF-I and IGF-II in relation to colorectal cancer. Int J Cancer 83:15–17
27. Jenkins PJ et al (2000) Insulin-like growth factor I and the development of colorectal neoplasia in acromegaly. J Clin Endocrinol Metab 85:3218–3221

28. Suikkari AM et al (1988) Insulin regulates the serum levels of low molecular weight insulin-like growth factor-binding protein. J Clin Endocrinol Metab 66:266–272
29. Bitni-Schnetzler M (1990) Insulin regulates the expression of the insulin-like growth factor binding protein 2 mRNA in rat hepatocytes. Mol Endocrinol 4:1320–1326
30. Giovannucci E (1995) Insulin and colon cancer. Cancer Causes Control 6:164–179
31. Brada M et al (1992) Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. BMJ 304:1343–1346
32. Tsang RW et al (1993) Glioma arising after radiation therapy for pituitary adenoma. A report of four patients and estimation of risk. Cancer 72:2227
33. Minniti G et al (2005) Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. J Clin Endocrinol Metab 90:800–804
34. Ayuk J, Stewart PM (2009) Mortality following pituitary radiotherapy. Pituitary 12:35–39
35. Coeli CM et al (2005) Incidência e mortalidade por câncer de tireóide no Brasil. Arq Bras Endocrinol Metab 49:503–509
36. Wexler TL et al (2010) Growth hormone status predicts left ventricular mass in patients after cure of acromegaly. Growth Hormon IGF Res 20:333–337