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Symptoms and signs of acromegaly: an ongoing need to raise awareness among healthcare practitioners

Redzuan Zarool-Hassan MBChB;¹ Helen M Conaglen PhD;² John V Conaglen MBChB, FRACP, MD;² Marianne S Elston MBChB, FRACP, PhD^{1,2}

ABSTRACT

INTRODUCTION: Chronic excess growth hormone production results in acromegaly, a condition associated with widespread physical changes, including soft tissue and bony overgrowth. When untreated, acromegaly reduces life expectancy. Patients usually remain undiagnosed for years after the onset of symptoms, by which stage irreversible physical changes have often occurred.

METHOD: A cross-sectional questionnaire study involving patients with acromegaly from the Waikato Endocrine Unit and the New Zealand Acromegaly Society evaluated features of acromegaly that were present before diagnosis. The aim of this study was to identify acromegaly features that were most prevalent to promote increased awareness about the disease by healthcare providers.

RESULTS: 81 participants were included. The main pre-diagnosis physical changes participants reported were acral changes, alterations in facial features and oral symptoms. For some, these features were present for more than 10 years before the acromegaly diagnosis. Multiple co-morbidities associated with acromegaly were reported. Two-thirds of the participants felt that an earlier diagnosis was possible. Most participants were in contact with General Practitioners (GPs) and/or dentists before diagnosis. Endocrinologists had the highest diagnosis rate, followed by GPs. Dentists had a low diagnosis rate despite a high prevalence of oral symptoms among study participants.

CONCLUSION: Increased awareness of acromegaly among primary care clinicians is important as they are the first-point-of-contact with the healthcare system for most patients. Health professionals' early recognition of symptoms and signs of acromegaly would reduce delays in time-to-diagnosis, enable earlier treatment and may improve outcomes for patients with acromegaly.

MESH KEYWORDS: Acromegaly; symptoms; delayed diagnosis; clinicians; primary healthcare

Introduction

Acromegaly is invariably due to excess growth hormone (GH) secreted by a pituitary adenoma and results in increased serum insulin-like growth factor I (IGF-I) levels. Excess GH exposure is characterised by end-organ effects, in particular, soft tissue and bony overgrowth. Acromegaly is rare, with a reported annual incidence of 3–4 per million and a population prevalence of 60 per million, although more recent studies suggest that the prevalence may be much higher.¹ This, coupled with insidious disease progress and non-specific symptoms, often leads to a marked delay in diagnosis, reported to range between 5 to 10 years after onset of symptoms.² Despite technological advancement in diagnostic methods to detect the disease, a delay in diagnosis continues to be ¹Department of Endocrinology, Waikato Hospital, Private Bag 3200, Hamilton, New Zealand

² Waikato Clinical Campus, University of Auckland, Hamilton 3240, New Zealand

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CORRESPONDENCE TO: Dr Marianne S Elston

Department of Endocrinology, Waikato Hospital, Private Bag 3200, Hamilton 3240, New Zealand Marianne.Elston@ waikatodhb.health.nz

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WHAT THIS GAP FILLS

What we already know: Acromegaly, characterised by chronic excess growth hormone production, results in widespread soft tissue and bony overgrowth, and is associated with premature mortality. Disease onset is insidious and diagnosis is often delayed many years after symptom onset.

What this study adds: Despite advances in medicine, patients with acromegaly are still diagnosed late, usually 5–10 years after symptom onset and frequently >10 years. Adults reporting enlargement of the hands and feet and/or altered facial morphology with increased jaw size should trigger consideration of acromegaly and measurement of an IGF1 level.

an issue due to under-recognition of the clinical features by health professionals.³

The diagnosis of acromegaly requires clinicians to consider the possibility of this disorder and measure a serum IGF-1 level, which will usually confirm or exclude the diagnosis. Confirmatory blood testing includes assessment of GH suppression following an oral glucose load followed by assessment of other pituitary hormones, tumour size by MRI imaging and co-morbidities such as visual field loss.

When untreated, acromegaly is associated with an increase in mortality, such that patients with uncontrolled GH excess die on average 10 years younger than predicted.² Acromegaly is also associated with cardiovascular, cerebrovascular, metabolic, orthopaedic, ophthalmic and respiratory co-morbidities as well as increased rate of various malignancies,4 which have a detrimental impact on patients' quality of life. Many of these changes, in particular osteoarthritis, are irreversible even with correction of GH excess.5 Therefore, early diagnosis of acromegaly is important and improves outcomes, including reducing overall mortality risk.6 Timely diagnosis also enables earlier intervention for the co-morbidities associated with acromegaly, consequently preventing progression to more advanced disease.

Acromegaly is a condition in which earlier diagnosis could be enabled by greater awareness of acromegaly symptoms and greater collaboration between general practitioners (GPs) and dentists. There is no formal integration of care between dentists and GPs: patients usually attend their GP for health-related symptoms and are sometimes referred to a hospital consultant if needed. Patients with dental symptoms may see a dentist, but there is no routine communication between dental and general practice services.

The aim of this study was to identify features of acromegaly that were most prevalent among patients at diagnosis. By drawing attention to these findings, an increased awareness of the features of acromegaly by health care professionals may be facilitated, enabling earlier diagnosis and treatment.

Methods

Patients with acromegaly were identified from the Waikato Endocrine Department and The New Zealand Acromegaly Society. Patients were invited to participate in the study at face-to-face routine clinic visits, by mail and email. The Waikato Clinical School summer studentship committee peer reviewed the project. The study was of minimal risk and therefore did not require formal ethics review. It was conducted in accordance with the National Health Advisory Committee's Ethical Guidelines for Observational Studies, and with permission of the Waikato Endocrine Department.

Questionnaires were distributed to 98 participants in either hardcopy or online (via a GoogleTM Documents hyperlink) during the period November 2012 to July 2014. Sixty-five questionnaires were distributed to members of the New Zealand Acromegaly Society; the remainder to patients seen in clinic at the Waikato Endocrine Department. Data received were anonymous.

The online questionnaire was in sections covering pre-designated domains that required responses before participants proceeded to subsequent sections of the questionnaire. This encouraged participants to answer all questions and increased rates of response for each domain. However, it was not possible to apply such techniques to paper questionnaires. Therefore, the number of responses to each question has been reported to enable meaningful evaluation and interpretation of response. As recall bias may be a limiting factor of reliable symptom reporting we also determined the reported time between diagnosis and questionnaire completion.

All completed questionnaires were collated in Microsoft Excel ©, then analysed using Statistica Version 11 (Statsoft Inc., Tulsa, OK, USA).

Results

Demographics

The response rate was 83% (81/98). A total of 83 responses were received during the study period, but 2 were excluded as they were duplicates. Of the 81 participants, 12 (15%) completed the questionnaire online and 69 (85%) completed the hardcopy questionnaire.

Participants were 51% female, 48% male (1 unspecified gender entry). Mean age was 58.6 years (s.d. 13.2 years). Patients aged 61–70 years formed the largest group. Ethnicity was reported in 78 patients: 64 (82%) were of New Zealand European descent. Median time since diagnosis was 7 years (range 0–47 years).

At the time of diagnosis, most participants were aged 41 to 50 years (Figure 1). The duration of symptoms is shown in Figure 2 and Table 1. Most patients had symptoms 5–10 years before diagnosis and 26% of patients had symptoms for over 10 years.

Diagnosis of Acromegaly

Concerns raised by a doctor or other health professional prompted the diagnosis of acromegaly in 42/80 participants, patient concerns in 24/80 and from a family member in only 2/80. Multiple factors led to diagnosis in 13/80. Two-thirds of participants (48/72) reported that they considered an earlier diagnosis could have been possible.

Almost all participants had visited their GP before the diagnosis of acromegaly was made, and dentists were the second-most visited health professional in this study. Other health professionals visited by the participants are shown in Table 2. Endocrinologists were reported to be the health professionals most likely to confirm the diagnosis of acromegaly.

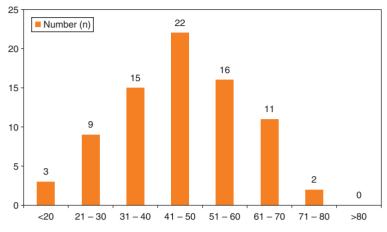
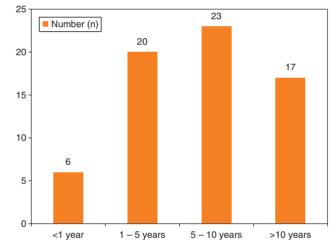


Figure 1. Age at diagnosis of acromegaly; Rate of response = 78 (96%)

Figure 2. Duration of symptoms before diagnosis; Rate of response = 66 (81%)



Participants also provided feedback into their experience before being diagnosed with acromegaly as shown in Table 3, where there were common themes around diagnostic delay and feelings of frustration with the healthcare system.

Features of Acromegaly and Co-Morbidities at Time of Diagnosis

Symptoms triggering medical attention and subsequent diagnosis of acromegaly are detailed in Table 4. Some participants provided more than one answer to this section. The most common symptoms were related to acral overgrowth, namely an increase in hand, foot and/or shoe size, as well as facial feature changes. Symptoms due to mass effects of the pituitary adenoma,

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Features Present Prior to	Yes (%)	RoR	RoR%		Duration o	f Symptoms	
Diagnosis		(N)	(N/81x 100)	<1 year (%)	1–5 years (%)	5–10 years (%)	>10 years (%)
Shoe size increase	62 (83)	75	93	0	19 (50)	14 (37)	5 (13)
Foot enlargement	60 (82)	73	90	0	20 (55)	13 (36)	3 (8)
Facial feature changes	52 (79)	66	82	2 (6)	21 (62)	6 (18)	5 (15)
Hand enlargement	59 (79)	75	93	0	21 (48)	17 (39)	6 (14)
Fatigue/tiredness	53 (73)	73	90	3 (9)	15 (43)	6 (17)	11 (31)
Glove tightness	42 (66)	64	79	0	13 (54)	7 (29)	4 (17)
Snoring	51 (65)	79	98	0	11 (35)	13 (42)	7 (23)
Increased skin tags	50 (64)	78	96	*	*	*	*
Diaphoresis	49 (64)	77	95	*	*	*	*
Daytime somnolence	44 (62)	71	88	3 (12)	8 (32)	8 (32)	6 (24)
Thick skin	45 (59)	76	94	*	*	*	*
Weight gain	46 (58)	79	98	*	*	*	*
Arthralgia	45 (57)	79	98	*	*	*	*
Jaw/forehead enlargement	41 (57)	72	89	2 (8)	13 (52)	6 (24)	4 (16)
Headaches	44 (54)	81	100	2 (6)	16 (50)	6 (19)	8 (25)
Oligomenorrhoea ($n = 41$)	21 (54)	39	95	*	*	*	*
Tongue size increase	40 (51)	79	98	2 (8)	16 (64)	5 (20)	2 (8)
Bite change	28 (49)	57	70	1 (7)	8 (53)	3 (20)	3 (20)
Acne/oily sweating	37 (47)	78	96	*	*	*	*
Pins & needles	36 (47)	77	95	*	*	*	*
Voice deepening	32 (42)	76	94	1 (5)	10 (50)	7 (35)	3 (10)
Increased tooth gap	31 (42)	74	91	1 (6)	10 (56)	3 (17)	4 (22)
Mood changes	29 (37)	78	96	*	*	*	*
Hirsutism	28 (36)	78	96	*	*	*	*
Sinus problems	27 (34)	78	96	*	*	*	*
Vision problems	25 (32)	78	96	4 (22)	6 (33)	5 (28)	3 (17)
Increased muscle mass (n = 43)	13 (30)	43	100	*	*	*	*
Alopecia	22 (28)	78	96	*	*	*	*
Hearing loss	14 (18)	79	98	*	*	*	*
Increased height	12 (16)	76	94	*	*	*	*
Erection dysfunction ($n = 39$)	5 (14)	37	95	*	*	*	*
Galactorrhoea	9 (12)	75	93	*	*	*	*
Infertility and problems conceiving	8 (11)	72	89	*	*	*	*

Table 1. Summary of features present before diagnosis (in order of frequency)

RoR = Rate of response.

Responses not collected as these symptoms were deemed not specific to acromegaly only.

such as headaches and vision disturbance were reported in 54% and 32% of the participants, respectively. Table 1 lists features present before diagnosis in order of prevalence as reported by study participants. The co-morbidities present in study participants are listed in Table 5. Arthritis was the most prevalent co-morbidity reported by participants, followed by bowel polyps, hypertension and hypercholesterolaemia.

Discussion

This study highlights that most patients have symptoms for many years before the diagnosis of acromegaly. It was extremely uncommon for the diagnosis to be made within one year of symptom onset. The fact that most participants had visited GPs and dentists before their diagnosis implies that these clinicians had the opportunity to detect patients with acromegaly earlier than others. Therefore, given their role as gatekeepers of the healthcare system, awareness of acromegaly is important in allowing prompt diagnosis of patients and early referral for treatment.

Participants identified three salient physical features of acromegaly, namely acral changes (enlarging hands and/or feet), altered facial features (e.g. prominent brow, increased jaw) and oral symptoms (increased size of tongue, splaying of teeth and altered bite). These symptoms can be identified from history and physical examinations during clinic visits. A third of participants (37%) were investigated further after presenting with a chief complaint related to acral changes. Concern from doctors and other health professionals was the major factor prompting diagnosis of acromegaly among half of participants.

Facial and oral symptoms were common and can continue unnoticed for many years due to the subtlety of facial feature changes, that patients themselves fail to identify until much later during the disease course. Even patients' regular clinicians may miss these symptoms in early visits before diagnosis. In fact, two participants who regularly saw their GPs were diagnosed only Table 2. Health professionals visited by participants before diagnosis and number of diagnoses made

Health Professional	Clinicians Seen by Patients before Diagnosis N (%)*	Clinicians who Diagnosed Participants N (%)*
General practitioners (including 2 locums)	63 (91)	18 (24)
Dentist	28 (42)	1 (1)
Eye specialist	21 (33)	1 (1)
Endocrinologist	18 (31)	22 (29)
Orthopaedic surgeon	14 (23)	4 (5)
Cardiologist	10 (17)	0
Sleep/respiratory specialist	10 (14)	2 (3)
Gynaecologist	5 (–)	1 (1)
Otorhinolaryngologist	3 (-)	4 (5)
Gastroenterologist	3 (–)	0
Diabetologist	2 (3)	0
General surgeon	2 (–)	1 (1)
Dermatologist	1 ()	0
Neurologist	1 ()	2 (3)
Neurosurgeon	1 ()	1 (1)
Oncologist	1 ()	0
Psychiatrist	1 ()	0
Rheumatologist	1 (–)	1 (1)
Vascular surgeon	1 ()	1 (1)
Emergency Department Physician	t	1 (1)
Maxillofacial surgeon	t	1 (1)
Other allied health professionals	t	4 (5)
Unspecified [‡]	t	10 (13)

* Percentage calculated by rate of response in each group.

[§] Data not assessed due to low numbers of replies.

Patients not providing responses to this section of questionnaire.

[‡] Unspecified clinicians where patients provide name of clinicians without stating speciality, and clinicians were unidentifiable through the Medical Council of New Zealand Clinician Database.¹⁴

Themes	Comments
Diagnostic delay due to unawareness	'I suffered for (at least) 10 years with symptoms of acromegaly before diagnosis was made. Early diagnosis would have saved me much discomfort.'
of own symptoms	'I should have realised I was unwell, especially as I had read an article in the newspaper in October 1994 on the condition.'
	'It appears I could have had the condition for 10 years or more but symptoms were ignored as (they were) possibly 'age-related' problems.'
Frustration with healthcare practitioners	'I have found myself really angry at his (GP's) dismissive attitude to a lot of my symptoms over the years – but I'm trying to forgive him. Nevertheless, I do believe he should have diagnosed my condition earlier.'
	" I took a list of my symptoms to my GPshe didn't follow up on it. I feel most let down by the ears, nose and throat specialistwho didn't ask about my hands and feet, and simply diagnosed (me with) weak vocal chords and sent me to a speech therapist."
	'I did mention my enlarged hands and feet to my doctor on one occasion (but) he did not make any comment.'

Table 3. Comments from participants related to acromegaly diagnosis

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Table 4. Symptoms of acromegaly that triggered diagnosis

Symptom	Number of Positive Responses (n)
Change in face only noticed by you	1
Change in face only noticed by another person	4
Change in hands &/or feet noticed by you	9
Change in hands &/or feet noticed by another person	10
Change in face AND hands &/or feet noticed by you	6
Change in face AND hands &/or feet noticed by another person	7
Visual loss	7
Neurological symptoms	16
Fertility issues	8
Arthritis	6
Other	26
Total Number of Responses	100

Table 5. Co-morbidities present at the time of diagnosis (in order of frequency)

Number (%)
40 (50)
35 (43)
34 (42)
32 (41)
28 (35)
23 (29)
22 (28)
17 (23)
18 (22)
15 (19)
6 (8)
5 (6)
5 (6)

after chance encounters with locum GPs, visited for reasons unrelated to acromegaly. Diagnosis appeared to be made earlier in patients presenting with facial symptoms compared to acral symptoms. This is possibly because facial changes were more obvious (and perhaps more debilitating) and noticed earlier than changes in their hands and/or feet.

Acromegaly is associated with multiple comorbidities resulting in multi-organ symptoms.^{3,4} Therefore treating clinicians need to be aware that the more common co-morbidities of acromegaly, such as arthritis or hypertension, may well be a hallmark of acromegaly and should raise suspicion if patient profiles fit with the disease characteristics.

In this study, endocrinologists were the clinicians most likely to make the diagnosis of acromegaly, e.g. when seeing a patient for thyroid disease. This is most likely due to an increased awareness of the condition among endocrinologists (as would be expected). GPs were the second most likely group to diagnose patients with acromegaly. Despite being the second-most visited healthcare professional in our cohort, and given that half of participants report oral symptoms, dentists were reported to have made the diagnosis for only one patient. These findings are comparable to another study investigating medical professionals visited by patients before diagnosis and their rate of diagnosing acromegaly.⁷ Siegel *et al.* also reported that despite a third of patients with acromegaly seeking care from dentists, the diagnosis was not considered.⁸ This raises the question of whether adequate awareness about acromegaly is present among dentists, despite the prevalence of oral symptoms in patients with the disease.

One limitation of the current study is that participants' responses were not confirmed with patients' medical records, so results may be affected by recall bias. In some patients several decades had passed since diagnosis so this is likely to have influenced recall and potentially accuracy of some answers.

Several methods to assist screening for acromegaly have been proposed. In a primary healthcare study, 17000 patients were screened using a questionnaire that evaluated enlargement of extremities.9 Although pre-test probabilities of the questionnaire were not made available, the authors proposed that screening based on phenotypic changes is cost-effective. However, population screening for acromegaly using biochemical assays have a low detection rate and incur unnecessary costs.¹⁰ In the DETECT study, among 6773 adult primary care patients in whom an IGF-1 measure was performed, 125 patients or 1.85% of the study population had elevated IGF-1 levels necessitating further evaluation. Of those, seven had investigation results consistent with acromegaly; (one patient was previously known to have acromegaly,

for two patients testing led to a new diagnosis and four had biochemistry consistent with the diagnosis but declined further testing). Of the remainder, 42 had acromegaly excluded and 76 had indeterminate results. It is uneconomical to perform routine IGF-1 testing on every patient in general practice given the low prevalence of acromegaly in the population (a single IGF-1 test costs approximately NZD57.00 as at November 2014).¹¹ Furthermore, unnecessary routine testing may also lead to patient anxiety and thereby cause harm.

In recent years, new methods have been devised to improve the detection rate of acromegaly, including computerized face detection.¹² A software program has been shown to have a higher accuracy in detecting acromegalic facial features than medical experts or general internists especially among patients with mild acromegaly.¹³ Although a promising tool, such techniques are not currently feasible to detect acromegaly in primary care due to cost restraints and lack of equipment availability. Use of this in a New Zealand population has also not been assessed and the sensitivity and specificity may differ for patients from various ethnic backgrounds.

Ultimately, raising awareness of acromegaly among primary healthcare clinicians remains a simpler yet more practical approach to improving the early diagnosis of the disease. Simple measures such as handouts, awareness campaigns and close relations with local acromegaly societies may still be the most effective approaches. Both medical and dental schools could also emphasise the disease in their curriculum. We recommend that if the diagnosis of acromegaly is entertained when meeting a patient, that further questioning should be performed and any suggestive symptoms should result in measurement of a serum IGF-1 or a phone call to the local endocrine team for advice.

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CONFLICT OF INTERESTS The authors report no conflict of interest in this study.