Impact of musculoskeletal disease on quality of life in long-standing acromegaly

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Abstract

Objective: To provide rheumatological assessment of patients with long-standing acromegaly and investigate the impact of musculoskeletal disease on quality of life.

Design: Cross-sectional observational study.

Methods: Fifty-eight patients diagnosed with acromegaly at least 5 years previously were interviewed and examined by a rheumatologist. Each patient completed the short form-36 (SF-36), arthritis impact measurement scales 2 (AIMS2) and acromegaly quality of life questionnaires (AcroQol).

Results: Fifty-two out of 58 (90%) reported musculoskeletal pain, with 29 (50%) reporting neck pain. Hip osteoarthritis was present in 49 (84%) and knee osteoarthritis in 20 (34%). Half the patients (52%) reported sleep disturbance, but only 2 (3.5%) had fibromyalgia. Ten (17.2%) had previously undergone carpal tunnel decompression. Fifty-one (88%) patients had consulted their general practitioner and 31 (54%) complementary therapists. SF-36, AIMS2 and AcroQol scores were lower in patients with musculoskeletal pain.

Conclusions: This study of musculoskeletal problems in patients with acromegaly reports systematic rheumatological examination, use of medical services and quality of life scores. Musculoskeletal problems should be routinely addressed in acromegaly by both endocrinologist and rheumatologist and a multidisciplinary approach taken to management.

Introduction

A number of studies have documented clinical features of acromegalic arthropathy (1–7) but little has been published on how this affects physical function and quality of life and there are no studies detailing systematic rheumatological examination of such patients. In a review of 45 case notes and 20 patients with acromegaly, 22% male and 36% female patients were moderately to severely disabled by their arthropathy (8). A good response to treatment, assessed clinically and by growth hormone (GH) estimation, was associated with better employment and less severe joint disease. Biermasz et al. evaluated both short form 36 (SF-36) and acromegaly quality of life (AcroQol) and first reported that patients with joint problems and controlled acromegaly had poorer QoL (9).

Various factors would be expected to influence long-standing changes of acromegalic arthropathy, such as cartilage hypertrophy and duration of uncontrolled GH and insulin-like growth factor 1 (IGF1). Control of IGF1 and GH by somatostatin agonists has been shown to reduce joint thickness in acromegaly by ultrasonography (10, 11). High levels and long duration of excess growth mediators alone have not been shown to correlate with greater joint damage (1, 3, 12). Other factors will contribute to development and severity of acromegalic arthropathy, as in osteoarthritis, including age, gender, genetic factors, local biomechanics, injury, obesity, deformity and muscle weakness (13).

We investigated pain and joint disease in patients with long-standing acromegaly from a rheumatological perspective. Information was collected on employment, use of medical services, function and quality of life with a systematic rheumatological examination including joints, carpal tunnel compression and fibromyalgia. The latter was included in view of sleep abnormalities characterizing acromegaly (14). The effect of musculoskeletal pain on quality of life was explored using three questionnaires: SF-36 version 2 (15), arthritis impact measurement scales 2 (AIMS2) (16) and AcroQol (17).

Methodology

The study was conducted at Department of Endocrinology at The Churchill Hospital, Oxford and Department of Rheumatology at the Nuffield Orthopaedic Centre, Oxford.
**Study population**

The study population comprised patients under review at The Churchill Hospital with acromegaly diagnosed at least 5 years previously, anticipating they were more likely to have controlled acromegaly and irreversible joint changes. All eligible patients actively followed-up at the time that we could contact were invited to participate by letter. Non-responders were sent one further letter. All the participants were interviewed and examined by the same rheumatologist.

**Data collection**

Demographic data were collected from medical records including age at diagnosis, pre-diagnosis disease duration, treatment, and date of biochemical cure. This was estimated when a normal age-related IGF1 and normal GH curve (mean < 5 mU/l) were achieved and maintained until the date of the interview. Duration of uncontrolled acromegaly was calculated by summation of pre- and post-diagnosis disease durations from diagnosis to date of control, or to time of study interview if uncontrolled. Acromegaly was defined as uncontrolled if the GH curve and/or IGF1 were not within this normal range or had lapsed from a previously normal report.

Information on musculoskeletal disease at presentation was obtained from patient recall and medical records. Patients were asked about the presence of musculoskeletal pain at diagnosis and currently, symptoms of carpal tunnel syndrome (CTS), subjective sleep disturbance, use of medical services for musculoskeletal problems, referral for medical and surgical consultations or allied health professionals, further investigations and use of complementary therapies.

Clinical examination included body mass index and number of fibromyalgic tender points. Examination of each joint included pain, tenderness, joint swelling, loss of range of movement and presence of deformity. Lumbosacral movement was measured using a modified Schober Index and was defined as limited if <5 cm. Clinical evidence of CTS was sought by inducing paraesthesia in the distribution of the median nerve on percussion of the median nerve at the wrist (Tinel’s test) and sustained palmar flexion of the wrist (Phalen’s test).

**Quality of life assessments**

Participants were asked to complete the AIMS2 (16), the SF-36v2 (15) and the AcroQol (17). The SF-36 is a generic measure of health status in the form of a 36-item questionnaire, providing scores on eight domains of functioning and well-being: physical functioning, role physical, role emotional, social functioning, mental health, energy/vitality, pain and general health perception and two broad areas of subjective well-being: physical and mental health. Scores were compared with normative data for a UK population (18) and with those of 48 patients with non-functioning pituitary tumours of mean age 59 (s.d. 12) years from the Oxfordshire region (19).

The AIMS2 is a questionnaire developed to assess health status in subjects with rheumatic disease (16). It is generally used in rheumatoid and osteoarthritis and its use as a tool in acromegalic arthropathy was explored here. There are 12 scales addressing function and pain: mobility level, walking and bending, hand and finger function, arm function, self-care tasks, household tasks, social activity, support from family and friends, arthritis pain, work, level of tension and mood. It has a potential range of scales from 0 to 10, with the worst possible score of 10.

The AcroQol is a disease-specific questionnaire for acromegaly containing 22 items scored globally and divided into two scales evaluating physical and psychological aspects (17).

**Statistical analysis**

Data analysis was performed using SPSS for Windows version 12 (Chicago, Illinois 60606, US). The SF-36, AIMS2 and AcroQol were scored using standard procedures. Missing values were only replaced with the mean of other items in the relevant scale if all other items were present for the AIMS2 and the AcroQol, and if more than half were present for the SF-36, following the standard guidelines. AIMS2 scale scores were modified to adjust for co-morbidity according to the User’s Guide Data.

Data are presented as N (%) or mean (s.d.) as appropriate. Comparisons between groups were undertaken using χ² tests for categorical data and t-tests or Mann–Whitney tests for continuous data. Independent association of factors with the physical functioning domain of the SF-36 was explored with stepwise linear regression analysis. Statistical significance was taken at P<0.05 throughout.

**Results**

Eighty-six patients were identified from department records as fulfilling the inclusion criteria and 58 (67%) were recruited over 1 year. Figure 1 is a flow chart showing participation and reasons for non-participation. Participants and non-participants did not differ significantly in terms of age (mean (s.d.) 58.1 (10.4) vs 55.1 (14.0); t=1.10, P=0.32), gender (% female 52 vs 35; χ²=1.67, P=0.20) or age at diagnosis (mean (s.d.) 43.8 (11.5) vs 40.7 (17.7); t=0.84, P=0.41).

**Patient demographics**

Details of patient demographics are shown in Table 1. Thirty (51.7%) participants were female, 43% were in paid employment and 38% were retired. The mean (s.d.)
age was 58.1 (10.4) years. The mean duration of diagnosed acromegaly was 14.3 (7.1) years, with mean (S.D.) age at diagnosis of 43.8 (11.5) years. Forty-seven (81%) had controlled acromegaly and 11 (19%) were uncontrolled.

**Prevalence of musculoskeletal symptoms**

Of 58 patients, 30 (51.7%) were recalled of musculoskeletal symptoms at the time of diagnosis: this information had been recorded in 20 (66%) medical records. The mean estimated (S.D.) age of onset of musculoskeletal pain by 50 participants was 42 (14.4) (Table 1).

Fifty-two of 58 patients (89.7%) reported current musculoskeletal pain. Other disorders contributing to musculoskeletal symptoms at the time of the study were ankylosing spondylitis ($n=1$), recent mild trauma ($n=2$), previous spinal trauma ($n=1$) and CVA ($n=1$). Two patients had MEN 1 comprising hyperparathyroidism and acromegaly of which one had severe osteoporosis and multiple low-trauma fractures, contributing to significant musculoskeletal disability and pain. The current presence of musculoskeletal symptoms and control of acromegaly were not significantly related ($\chi^2 = 0.16$, df = 1, $P = 0.69$).

**Use of medical services**

Table 2 shows the medical services consulted for musculoskeletal symptoms. Fifty-one (87.9%) had sought help from their primary care physician about musculoskeletal pain and over half received physiotherapy. Thirty-one had sought complementary therapies for their pain including chiropractors, osteopaths and acupuncturists.

**Carpal tunnel syndrome (CTS)**

Ten (17.2%) had previous decompression surgery. Twenty-three (39.7%) had symptoms at diagnosis.
Eighteen (31%) had current symptoms and 12 (20.6%) had clinical evidence of median nerve compression when tested by Tinel’s and/or Phalen’s test.

**Fibromyalgia and non-restorative sleep**

Sleep disturbance was found to characterize half the study population \((n=29, 50\%)\), with half reporting waking unrefreshed \((n=30, 51.7\%)\). Eleven (19.0%) had been investigated with sleep studies. However, only 2 (3.5%), one male and one female, had clinical evidence of fibromyalgia indicated by the presence of more than ten fibromyalgic points.

**Results of examination**

The main sites of pain reported were in the neck (50% participants), low back (53%), hip (56.9%) and knee (48%). Hip pain was present in 28 patients (48.3%), but restricted hip movement, indicating osteoarthritis was present in 84.5% of the group. Knee pain was reported by 33 (56.9%) with objective evidence of knee arthritis by restricted knee movement in 34.5% and deformity such as swelling in 24%.

There was a reduced range of active cervical movement in 77.6%. Limited lumbosacral movement was present in only 2 (3.4%) including one with ankylosing spondylitis. The most commonly reported site of pain in the upper limb was the shoulder \((n=13, 22\%)\), but fewer \((n=9, 15.5\%)\) had a reduced range of shoulder movement, indicating probable referred neck pain. Deformities of the fingers were observed in 38% of the group.

**Questionnaires scores and comparison with scores from other studies**

Table 3 compares SF-36 mean (s.d.) scores from the study population with the population norms for individuals aged 55–59 from the Oxford Healthy Life Survey \((18)\) and with published results of scores for 48 patients with non-functioning pituitary tumours age 59 years \((s.d. 12\) years) from the Oxfordshire region \((19)\). These groups were of comparable mean age with our study group aged 58 \((s.d. 10\) years). Our study group SF-36 scores were poorer than those reported by these patients in all domains and significantly lower in the physical functioning, social functioning, pain and general health perception domains. SF-36 scores were significantly lower than the scores in the general population for all domains except role emotional and mental health with a \(P\) value <0.001.

Table 4 compares questionnaire scores between study patients with and without musculoskeletal pain for the SF-36, the AIMS2 and the AcroQol. Those with musculoskeletal pain, forming the much larger group, scored lower for all SF-36 domains except role emotional but reached statistical significance at \(P<0.05\) only for the domains of physical functioning, mental health and pain. Variables significantly independently associated with the SF-36 domain physical function were type of employment, subjective sleep disturbance and presence of musculoskeletal pain.

AIMS 2 scores were worse for the group with musculoskeletal pain for all domains except social activity and work, but were only statistically significant for pain, \(P<0.05\). Global, physical and psychological AcroQol scores were significantly poorer in the group with musculoskeletal pain. The duration of uncontrolled acromegaly was not significantly associated with any AIMS2, AcroQol, or SF-36 questionnaire score.

**Discussion**

This is the first detailed study of musculoskeletal problems encountered by patients with acromegaly, which utilises a systematic rheumatological examination. We identified those diagnosed with acromegaly longer than 5 years in order to evaluate the effects of long-term and irreversible arthropathy rather than the early reversible arthropathy. The study is limited by being cross-sectional but provides data on the impact of musculoskeletal problems on quality of life and the services utilized by these patients. While the SF-36 and AcroQol have been used before \((9)\), this study is the first to report on AIMS2 scores in acromegaly.

Biermasz et al. presented data on 118 acromegalic patients in long-term remission reviewing the prevalence of self-reported joint problems along with other morbidity \((9)\). Joint complaints were especially perceived to contribute to reduced quality of life. As with our study, the presence of joint problems was unrelated to normal GH parameters or active disease duration.

Our response rate was 67%. There were no significant differences between participants and non-participants in terms of age, gender or age at diagnosis, although participants tended to be older and female. The presence
of musculoskeletal pain was reported in 90% of participants, a higher proportion than the 70% reported in other studies (1, 2). This may reflect recruitment by written invitation asking the patient to participate in a study of musculoskeletal problems, although it was specified that those without should also participate. Nevertheless, the number with joint problems is high. Despite having acromegaly, a serious and chronic disease, more than half were in paid employment or running a family home and fewer than 10% relied on a sickness or disability pension.

Study numbers did not allow sub-analysis of whether types of treatment for acromegaly (surgical, radiotherapy, medical or combination) or the need for replacement therapy with hydrocortisone, oestrogen or progesterone or thyroxine, was associated with rheumatological outcome. Only 66% of those recalling musculoskeletal symptoms at diagnosis had this information recorded in their medical notes, perhaps indicating less attention paid to this aspect of their symptoms at clerking. Most patients reporting current musculoskeletal pain had sought help from their general practitioner but only half had been referred for physiotherapy. Almost 60% had sought complementary therapies for their pain. The use of complementary and alternative medicine (CAM) is common in rheumatological patients. Holden et al. reported 44% follow-up rheumatology outpatients in three UK centres had used herbal or over the counter remedies in the previous 6 months (20), with the risk of unforeseen drug interactions and Rao et al. found 90% of 146 rheumatology patients had used CAM at some time (21).

Similarly to previous reports, 17% had undergone carpal tunnel release prior to diagnosis of their disease (9). CTS, although classically associated with the initial phase of acromegalic arthropathy, was present in 31% of this group, indicating it may be a longer term problem requiring further treatment.

A high proportion of patients reported neck pain and had reduced range of cervical movement. In some, neck pain was referred to the shoulder or elbow, resulting in joint pain without evidence of local arthritis. Low back pain was also reported but a modified Schober index was not found to be a useful indicator of reduced mobility. Knee pain was the most commonly reported joint problem and clinical evidence of hip osteoarthritis the commonest examination finding. Referred pain from hip to knee may account for some reported knee pain.

Studies of sleep apnoea in acromegalics have demonstrated both upper respiratory obstruction and central components (14). Even those without sleep apnoea have a profound reduction in the amount of rapid eye movement (REM) sleep time (22). Non-organic muscle pain is attributed to non-restorative sleep in rheumatoid patients (23). In view of these sleep disturbances in

| Table 4 Questionnaire scores in acromegalic patients with and without musculoskeletal pain. |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| SF-36 domain | With pain | Without pain | Mann–Whitney P value |
| N | Mean (s.d.) | N | Mean (s.d.) |  |
| Physical functioning | 52 | 62.5 (30.1) | 6 | 86.3 (12.4) | 0.040 |
| Role physical | 52 | 63.5 (31.60) | 6 | 85.4 (14.6) | 0.131 |
| Role emotional | 52 | 76.6 (28.2) | 6 | 76.4 (28.1) | 0.832 |
| Social functioning | 52 | 76.2 (24.9) | 6 | 83.3 (20.4) | 0.558 |
| Mental health | 52 | 71.4 (17.0) | 6 | 86.7 (12.9) | 0.033 |
| Energy/vitality | 52 | 49.4 (22.1) | 6 | 65.6 (22.3) | 0.153 |
| Pain | 52 | 56.6 (27.1) | 6 | 96.3 (5.7) | 0.000 |
| General health perception | 49 | 54.6 (19.6) | 6 | 62.3 (32.0) | 0.803 |
| AIMS2 | | | |
| Mobility | 50 | 1.04 (1.54) | 5 | 0.20 (0.27) | 0.282 |
| Walking and bending | 49 | 2.38 (2.48) | 5 | 1.10 (1.03) | 0.241 |
| Hand and finger function | 50 | 0.38 (0.82) | 5 | 0 (0) | 0.256 |
| Arm function | 49 | 0.45 (1.11) | 5 | 0 (0) | 0.217 |
| Self-care | 50 | 0.40 (1.36) | 5 | 0 (0) | 0.619 |
| Household tasks | 50 | 0.50 (1.34) | 5 | 0 (0) | 0.432 |
| Social activity | 49 | 4.06 (1.92) | 5 | 4.6 (2.1) | 0.504 |
| Support from family | 46 | 2.03 (2.48) | 4 | 0.47 (0.94) | 0.164 |
| Arthritis pain | 48 | 3.01 (2.89) | 5 | 0.08 (0.17) | 0.002 |
| Work | 24 | 1.12 (1.58) | 3 | 1.67 (1.44) | 0.532 |
| Level of tension | 48 | 2.30 (1.68) | 5 | 1.33 (2.1) | 0.112 |
| Mood | 48 | 1.90 (1.39) | 5 | 1.48 (1.39) | 0.524 |
| AcroQol | | | |
| Global score | 52 | 59.1 (16.0) | 6 | 75.8 (13.2) | 0.018 |
| Physical score | 52 | 59.9 (20.9) | 6 | 79.7 (13.7) | 0.028 |
| Psychological score | 52 | 58.5 (17.3) | 6 | 73.5 (13.8) | 0.047 |
acromegaly, it was anticipated that a number of participants might have evidence of fibromyalgia. However, despite the high incidence of sleep disorders and reports of non-restorative sleep, very few had fibromyalgia, refuting non-organic pain as an important contributor to musculoskeletal problems in acromegaly.

The questionnaires demonstrate an association between musculoskeletal disease and reduced quality of life in acromegalic patients. In the study by Biermasz et al., SF-36 and AcroQol scores were significantly lower in patients with joint-related complaints (9). Similarly, our study also demonstrated that those reporting musculoskeletal symptoms had lower SF-36 scores for all domains except role emotional and lower AcroQol scores. Participants reporting pain had lower AIMS2 scores in domains specifically addressing function and mobility, such as household tasks and level of tension, as well as those directly related to pain. Statistical significance was reached in comparisons for SF-36 physical functioning, mental health and pain, for AIMS2 pain and for physical and psychological AcroQol scores. Patients with acromegaly scored poorly in questions associated with physical function, indicating on-going ill health despite treatment for over 5 years. Their scores for mood and mental health were comparable with a normal population (15).

**Clinical implications**

Barkan emphasized that among more than 100 acromegals, virtually every case of severe disability was due to arthropathy, and at least 30% of patients have moderate or severe arthritic complaints (24). Musculoskeletal pain is a frequent problem encountered in acromegaly and is associated with a reduction in quality of life. Patients with acromegaly should be routinely asked about musculoskeletal problems and an active approach taken to addressing pain and functional difficulties. This would include advice on analgesia, physiotherapy, occupational therapy, advice on footwear and weight loss.

Referral for surgical intervention should be considered for those who fail to respond to conservative measures. Patient education is a vital aspect of improved pain and function and can be aided by the provision of written material including information leaflets produced by the Arthritis Research Council. While the use of comprehensive questionnaires such as the AIMS2 can be useful to assess interventions, it is time-consuming. In the clinical setting, a useful tool to screen for musculoskeletal problems is the GALS system (Gait, Arms, Legs, Spine), where validated questions and examination identify problem areas (25).

**Acknowledgements**

The authors would like to thank Dr Helen Turner and Prof. Raj Thakker for consenting to the inclusion of their patients in this study. This study was funded by a grant from the Oxford Health Services Research Committee. Ethical approval was received from the Oxford Research Ethics Committee.

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Received 20 January 2008
Accepted 26 January 2008