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Two phenotypes of arthropathy in long-term controlled acromegaly? A comparison between patients with and without joint space narrowing (JSN)

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ABSTRACT

Background: Arthropathy is an invalidating complication of acromegaly, also in long-term controlled patients, and is radiographically characterized by osteophytes and preserved joint spaces. However, joint space narrowing (JSN) is observed in the minority of patients. It is unknown whether JSN is the end-stage of acromegalic arthropathy or whether this feature develops independently of acromegaly.
Objective: To gain insight into the pathophysiology of acromegalic arthropathy, and, more specifically, in the process of JSN, risk factors for radiographic JSN were studied in a cross-sectional study.
Methods: We studied hips and knees of 89 well-controlled acromegaly patients (mean age 58.3 yr, 51% female). Joints were divided into two groups based on the presence of JSN, defined as an Osteoarthritis Research Society (OARSI) score ≥ 1. Potential risk factors for JSN were assessed, and its relationship to joint complaints. Individual knees and hips were analyzed in a Generalized Estimating Equations model, adjusted for age, sex, BMI and intra-patient effect.
Results: In controlled acromegaly, JSN was found in, respectively, 10.3% and 15.4% of the hips and knees. Increasing age and female sex were associated with more JSN; acromegaly-specific risk factors for JSN were joint-site specific. In the hip, JSN was related to more active disease: higher pre-treatment GH/IGF-1, longer and more severe GH exposure and immediate postoperative cure was less frequently achieved. In the knee, especially previous knee surgery, not acromegaly-specific characteristics, was associated with JSN. The presence of JSN was associated with more joint complaints.
Conclusions: JSN is an infrequent finding in patients with acromegalic arthropathy, but it is associated with more symptoms. This study indicates that, at least in the hip, early and ongoing GH/IGF-1 activity play a role in JSN development.

1. Introduction

Acromegaly is a chronic endocrine disease with high prevalence of arthropathy in active and cured disease, resulting in considerable functional disability [1]. It is suggested that increased exposure to insulin-like growth factor-1 (IGF-1), the main mediator of growth hormone (GH) action, is the driving mechanism in secondary osteoarthritis (OA) in acromegaly [2]. In a hypothetical model, acromegalic arthropathy has a bi-phasic pattern with initially reversible endocrine changes, followed by mechanical changes. First, elevated GH and/or IGF-1 levels promote the growth of articular cartilage and peri-articular ligaments, leading to cartilage hypertrophy with a limited range of movements. This early stage is thought to be, at least partially, reversible with adequate biochemical disease control. Subsequently, when GH excess persists, changes become irreversible. At this late stage, acromegalic joints acquire the characteristics of degenerative joint disease [3]. However, little clinical studies are available to support this hypothesis.

Previously, we have demonstrated that the prevalence of arthropathy is high, also in patients with long-term biochemical disease control [4]. These patients have a 4 to 12-fold increased risk to develop OA, even at very young ages, in comparison to the general population [5]. GH/IGF-1 activity at diagnosis is related to the prevalence of radiographic OA (ROA) [6]. Interestingly, despite long-term cure, the distribution of radiological abnormalities remained different from regular degenerative joint disease, *i.e.* primary OA. The radiographic phenotype in acromegaly is predominantly characterized by severe osteophytosis, frequently in combination with preserved normal or even widened joint spaces.

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Therefore, it is suggested that GH hypersecretion is especially involved in bone formation, but may protect against cartilage loss [7]. This observation conflicts with the previous hypothesis that there is a final common pathway with primary OA, at least in the majority of patients.

Nonetheless, a minority of acromegaly patients shows radiographic joint space narrowing (JSN), mimicking primary OA, instead of the characteristic joint space widening of acromegaly. This suggests that in acromegaly, there are two types of arthropathy: first, osteophytosis in combination with preserved/widened joint spaces, and second, in a small group, JSN with or without osteophytes. At present, the process of JSN is not fully understood, and it is unknown whether radiographic JSN is the end-stage of acromegalic arthropathy when the GH/IGF-1 excess has exceeded a critical threshold or whether it is a radiographic feature which develops independently of acromegaly, caused by, for example, high biomechanical forces or previous joint surgery.

In order to gain insight in the pathophysiology of acromegalic arthropathy and, more specifically, in the process of JSN, we compared patients with and without radiographic JSN in the knee and hip with respect to patient and treatment characteristics and physical stress. Both patients with and without JSN were derived from the same long-term controlled acromegaly cohort.

2. Methods

2.1. Patients

All consecutive patients with acromegaly, who were referred for treatment from 1977 onwards to the Leiden University Medical Center, were collected in a database. For the present study, 126 consecutive patients with long-term controlled acromegaly (defined as ≥2 yr) were invited for participation. Thirty-seven patients preferred not to participate for various reasons such as illness, travel distance, lack of time or psychological reasons. Consequently, 89 patients were included in the present analysis. The 37 non-included patients did not differ from the participating patients with respect to age, sex, BMI, active disease duration, pre-treatment GH/IGF-1 levels, type of treatment, follow-up duration and self-reported joint complaints [6].

Detailed yearly follow-up was performed from the onset of acromegaly treatment. The first treatment option in the majority of patients was transsphenoidal surgery (TPS) performed by a single specialized neurosurgeon. If necessary, adjuvant treatment consisted of radiotherapy (RT) (prior to 1985) or SMS analogs (from 1985 onwards). From 1998, some patients received depot formulations of long-acting SMS analogs as primary treatment. Since 2003, Pegvisomant was available for treatment-resistant acromegaly.

Disease activity was assessed yearly by oral glucose tolerance tests (except in medically treated patients), fasting serum GH and IGF-1 levels. Remission of acromegaly was defined as a normal glucose-suppressed serum GH < 1.25 (RIA assay until 1992) or 0.38 μg/l (immunofluorometric assay (IFMA) from 1992 onwards), serum GH levels of <1.9 μg/l (all years), and normal IGF-1 levels for age (from 1986 onwards) [4,8,9]. Patients not meeting these criteria were offered additional treatment.

Hypopituitarism was supplemented with thyroxine, hydrocortisone, and testosterone/estrogens according to the following definitions [10]. Estrogen deficiency in women was present in case of LH/FSH deficiency in premenopausal women with prolonged amenorrhea > 1 yr without adequate replacement therapy or by a low serum estradiol concentration of <70 nmol/l and all postmenopausal women. In men, LH/FSH deficiency was defined as testosterone level below the reference range (8.0 nmol/l). Thyroid stimulating hormone (TSH) deficiency was defined as a free thyroxine level below the reference range (<10 pmol/l). Adrenocorticotrophic hormone (ACTH) deficiency was defined as an insufficient increase of cortisol (peak < 0.55 μmol/l) after corticotrophin releasing hormone test or insulin tolerance test. GH deficiency was not routinely assessed.

Patients were seen at the outpatient clinic for a single visit. The study protocol was approved by the Medical Ethics Committee, and all subjects gave written consent.

2.2. Study parameters

2.2.1. Questionnaires

A standardized questionnaire was completed concerning demographic data, medical history, OA symptoms and signs and information on type of occupation and type of sport. Other relevant details of treatment and patient characteristics were derived from patient records.

2.2.2. Physical examination

Physical examination was performed by a single physician (M.W.) trained in structured joint assessment. Internal rotation and flexion of the hip and extension of the knees were assessed, in combination with both pain and crepitation.

2.2.3. Radiographic protocol

Radiographs were obtained from all patients between September and December 2007. Conventional radiographs of the knee (posterior–anterior (PA)), weight-bearing, fixed-flexion [11,12] and hips (PA, supine) were obtained from all patients, according to a standardized protocol with a fixed film-focus distance and fixed joint position. All radiographs were performed by a single experienced radiology technician.

2.2.4. Assessment of radiographic OA

For semi-quantitative assessment of the radiographic cartilage damage, JSN was graded in the knee (both medial and lateral femorotibial compartments) and hip on a scale from 0 to 3, using the Osteoarthritis Research Society (OARSI) atlas [13]. Radiographs were scored by consensus opinion of two experienced readers (M.W. & K.M.J.A.C.), blinded for patient characteristics. In cases of disagreement, the lower, more conservative score was adopted. The reproducibility for JSN in the hip and knee, reflected by the intra-class correlation coefficient (ICC), was good (0.89 and 0.82, respectively, for the hip and knee). The reproducibility was based on the repeat reading of 15 randomly selected radiographs. JSN was defined as an OARSI score of ≥1 at a particular joint site. Based on the presence of JSN, the patients were divided into two groups (*i.e.* OARSI ≥1 *vs* OARSI 0), independently for the knee and hip joint. Joint prostheses could not be scored with OARSI, and therefore, these joints (*i.e.* 3 knees, 2 hips) were excluded from the analyses.

Radiographic knee and hip OA were also scored according to the Kellgren–Lawrence (KL) scale, including other OA features, by a single experienced musculoskeletal radiologist (H.M.K.) [14]. ICCs were 0.89 and 1.00 for the knee and hip, respectively. Radiographic OA was defined as KL ≥ 2 or presence of a knee or hip prosthesis.

2.2.5. Definition of clinical OA

We used the clinical American College of Rheumatology (ACR) criteria for the assessment of clinical hip and knee OA. Criteria for clinical hip OA were pain in combination with internal rotation of ≥15° and morning stiffness for ≤60 min [15]. Clinical criteria for knee OA were pain, crepitation on physical examination and morning stiffness ≤ 30 min in combination with bony enlargements [16].

2.2.6. Parameters of acromegalic disease

Active disease duration was calculated from the estimated date of onset, using start of signs and symptoms, and facial changes on photographs to the date of normalization of serum IGF-1 levels after surgery or additional therapy. Remission duration was calculated from the date of normalization of serum IGF-1 concentrations until start of the