CLINICAL STUDY

The pathology of the ulnar nerve in acromegaly

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Abstract

Context: Acromegalic patients may complain of sensory disturbances in their hands. Cubital tunnel syndrome, the ulnar nerve neuropathy at the cubital tunnel (UCT), in acromegalic patients has never been reported.

Objective: To describe and assess the prevalence of UCT in acromegalic patients and the effects of 1 year of therapy on UCT.

Patients: We examined prospectively 37 acromegalic patients with no history of polyneuropathy, acute trauma at the elbow, no diabetes or hypothyroidism with clinical examination, nerve conduction studies (NCS), and high-resolution ultrasound (US). A control group was made by 50 volunteers. The local ethics committee approved the study and written informed consent was obtained from all subjects involved in the study.

Intervention: Clinical history, physical examination, NCS, and US were used to diagnose UCT at the beginning of the study and after 1 year.

Results: In 8 of 37 patients, a diagnosis of UCT was made at the beginning of the study reflecting a prevalence of 21%. After 1 year, 5 of 8 (62.5%) patients reported clinical and NCS improvements and evident US reduction of nerve cross-sectional area (CSA; $16.7 \pm 2.9 \text{ mm}^2$ vs $12.2 \pm 3.1 \text{ mm}^2$; $P < 0.001$). In 3 of 8 (37.5%) patients, the UCT was unchanged. Ulnar nerve CSA was significantly increased in acromegalic patients with UCT ($16.7 \pm 2.9 \text{ mm}^2$ vs $11.1 \pm 2.3 \text{ mm}^2$; $P < 0.047$).

Conclusion: Ulnar neuropathy could occur in acromegalic patients and can improve in 62% of cases with disease control. Due to the different management and therapeutic approach, it would be important to make differential diagnosis between cubital and carpal tunnel syndrome in acromegaly.

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Introduction

Carpal tunnel syndrome (CTS) is a common complication of acromegaly occurring in 20–64% of patients at diagnosis (1, 2). Sensory disturbances in the hand of acromegalic patients may derive from a generalized nerve swelling that involves the median nerve and the ulnar nerve (3). Ulnar nerve entrapment at the elbow (cubital tunnel syndrome, UCT) is the second most common peripheral nerve entrapment syndrome following CTS in the normal population. UCT is the cause of disability and pain for patients and, in extreme cases, may progress to loss of function of the hand (4). In the clinical practice, sensory disturbances typically affect acromegalic patients' hands, but the majority of investigations deal with median nerve involvement (1–5). In particular, Jenkins *et al.* elegantly demonstrated by magnetic resonance imaging that the predominate pathologic mechanism of median neuropathy in acromegaly seems to be edema of the perineural sheathes rather than increased volume of the carpal tunnel contents (5). However, to the best of our knowledge, in acromegaly little attention has been given

to ulnar nerve entrapment at the elbow which may determine altered sensation in the little and ring fingers and, in later stages, wasting of the small muscles of the hand and of the ulnar-side forearm (4). UCT is often misdiagnosed and the adjunct of ultrasound (US) to electrodiagnostic tests increases the sensitivity of the diagnosis to 98% (6). Differential diagnosis between CTS and UCT assumes clinical relevance due to the different management and therapeutic approach. Therefore, the aim of this study was to assess UCT in acromegalic patients at the baseline and after 1-year of treatment.

Materials and methods

Patients

We prospectively evaluated 37 acromegalic patients (18 females and 19 males, age range 18–79 years, disease duration range 1–15 years) and 50 healthy age-, sex-, and body mass index-matched controls with no history of polyneuropathy, acute trauma at the elbow, alcohol abuse,

vitamin B12 deficiency, diabetes or hypothyroidism, with clinical examination, nerve conduction studies (NCS), and US to identify the presence of ulnar neuropathy at the elbow. In these patients, the diagnosis of acromegaly was based on established criteria (7). At the beginning of the study, 6 patients had a new diagnosis (*de novo*) and did not receive any previous treatment, 21 previously underwent transsphenoidal neurosurgery (10 of these were also treated with somatostatin analogues), 9 underwent primary medical therapy with somatostatin analogues, and the remaining one underwent radiotherapy and medical therapy with octreotide. Disease activity was evaluated by growth hormone (GH) measurement during oral glucose tolerance test (OGTT) and the basal value of insulin-like growth factor 1 (IGF1), and the patients were subdivided into three subgroups according to established criteria (7): controlled ($n=17$), uncontrolled ($n=12$), and partially controlled ($n=8$) in whom a discrepancy among GH during OGTT and basal IGF1 values was noted.

The study was approved by the local ethics committee and written informed consent was obtained from all patients and controls.

Clinical examination

During physical examination the following in each patient were systematically assessed:

- 1) Pinprick sensation in the area of the ulnar digital, palmar cutaneous, and dorsal cutaneous sensory branches;
- 2) strength of the first dorsal interosseous, abductor *digiti minimi*, *flexor carpi ulnaris*, and *flexor digitorum profundus* muscles using the Medical Research Council rating scale; and
- 3) muscle bulk of the hypothenar and first interosseous space (6). Moreover, patients with clinical symptoms of CTS according to the American Academy of Neurology (8) were excluded from the follow-up.

Neurophysiological examination

Patients identified at physical examination with possible UCT underwent NCS to confirm the suspected diagnosis.

Motor nerve conduction velocities of the ulnar nerve were calculated from below the elbow to the wrist and along a more than 10 cm segment across the elbow. The median nerve was also evaluated to exclude a Martin–Gruber anastomosis. The diagnosis of ulnar neuropathy at the elbow was made following the criteria of the American Association of Electrodiagnostic Medicine: absolute slowing of nerve conduction at the elbow, decreased conduction velocity of more than 10 m/s across the elbow, decreased amplitude of more than 20%, absence of sensory responses, or evidence of muscle atrophy (9).

Ultrasonography

In order to increase the sensitivity of clinical examination and electrodiagnostic tests (10), we evaluated

the ulnar nerve with a broadband (17–5 MHz) linear array transducer. The adjunct of US to diagnose UCT increases the sensitivity and specificity of the diagnosis reaching values of 98% and it is recommended by the latest developments in neurology (10). US criteria for nerve identification were based on anatomical landmarks and detection of the fascicular echotexture (11). A swollen and hypoechoic ulnar nerve with the loss of the fascicular pattern at the cubital tunnel and a narrowing of the nerve as it entered the cubital tunnel were the US signs of ulnar entrapment at the elbow (Fig. 1). Moreover, ulnar nerve cross-sectional area (CSA) was evaluated considering the threshold value for cubital tunnel syndrome to be an area of 7.5 mm² (12).

Patients with a diagnosis of UCT at the beginning of the study were reevaluated after 1 year.

Laboratory assays

Circulating GH and IGF1 levels were determined as reported previously (13).

Statistical analysis

Statistical analysis was performed using SPSS 11.0 software (Chicago, Illinois, USA). Mann–Whitney *U* test was used for unpaired data to compare patients and controls as well as patients' groups. Wilcoxon signed-ranks test for related samples was used for comparison of the patient with UCT at the beginning of the study and after 1 year. *P* values < 0.05 were considered significant.

Results

Clinical examination

A total of 37 patients were evaluated. At the beginning of the study, 13 acromegalic patients were asymptomatic and 15 patients referred sensory disturbances related to

Figure 1 (a) Normal longitudinal 17.5 MHz US of the ulnar nerve at the cubital tunnel in a normal subject. (b) Evidently enlarged and swollen ulnar nerve in a symptomatic acromegalic patient at the elbow. In this patient, the ulnar nerve CSA on short-axis plane was 27 mm² (the normal cut-off value is 7.5 mm²).

the median nerve, and so these patients were excluded. The remaining nine patients (three *de novo*, two with uncontrolled acromegaly, one partially controlled, and three with controlled acromegaly) complained of sensory disturbances (numbness and paresthesias) in the territory of distribution of the ulnar nerve. Weakness or atrophy in first dorsal interosseous or *abductor digiti minimi* was noted in one of the nine patients. One of these nine symptomatic patients had sensory disturbances in the hand as a whole and has been excluded because NCS and US identified a CTS.

After 1 year, the eight patients with sensory disturbances in the territory of the ulnar nerve, and without CTS, have been evaluated again: 5 patients (one uncontrolled and four controlled, two of them *de novo* at the beginning) reported clinical improvement of the sensory abnormalities while 3 patients (two uncontrolled, one *de novo* at the beginning and one partially controlled) did not.

Neurophysiological examination

Patients identified at physical examination with possible ulnar neuropathy underwent NCS to confirm clinical data. In the $n=3$ of 8 patients with weakness or atrophy NCS confirmed the diagnosis of UCT, while in 5 of 8 cases NCS were normal. In the $n=1$ patient with diffuse sensory disturbances in the hand, UCT was excluded but a mild (abnormal digit/wrist sensory nerve conduction velocity and normal distal motor latency) CTS was diagnosed.

After 1 year, $n=6$ of 8 patients had a normal NCS while $n=2$ of 8 patients had no changes in the electrophysiological examination.

In 14 of 15 acromegalic patients excluded from the study with sensory disturbances in the territory of the median nerve, a CTS was confirmed by NCS and none of these patients had a concomitant UCT.

Ultrasonography

Nine patients with symptoms related to the ulnar nerve were evaluated at the beginning of the study and after 1 year. Nerve CSA was over the cut-off value in all of these nine patients. In eight of them, a swollen ulnar nerve at the cubital tunnel level was found on the side corresponding to the symptoms reported. The ulnar nerve narrowed at the entrance into the cubital tunnel and the ulnar nerve appeared swollen and enlarged with the loss of the fascicular pattern proximal to the cubital tunnel. The remaining one had US signs of nerve compression consistent with a CTS.

After 1 year, in the five patients (62%) who reported a clinical improvement, there was an evident reduction of the ulnar nerve CSA. In three patients without clinical improvement, the CSA and overall US appearance of ulnar nerve remained unchanged or increased ($n=1$). Intra- and inter-observer variability for the US measurements were both good (K values: 0.91 and 0.93).

Concordance with clinical examination, NCS, and US

Based on the results of these three approaches, we diagnosed UCT in eight patients (Table 1). One patient with sensory disturbances on the hand as a whole was considered as a CTS with a 'glove' distribution of paresthesias (14) and was excluded. We considered also the five patients with normal NCS and abnormal US as having UCT because, especially in mild UCT, NCS may be normal and US increases the sensitivity of electrodiagnostic tests (4–6). Therefore, in our series, the prevalence of UCT was 21%, whereas the prevalence of CTS was 40%.

Asymptomatic acromegalic patients had an increased nerve CSA at the cubital tunnel in comparison with controls ($P<0.001$), and symptomatic acromegalic patients had the bigger ulnar nerve CSA than these two groups ($P<0.047$). The results are summarized in Table 2, and an exemplary case is depicted in Fig. 2.

No differences were observed between men and women and patients treated with somatostatin analogues and patients submitted only to radiotherapy or neurosurgery.

There were no patients with UCT who had a concomitant CTS.

Discussion

The results of the study show that 1) sensory disturbances in acromegalic patients' hands could be related to ulnar nerve entrapment at the elbow and not only to CTS; 2) UCT in acromegalic patients has a prevalence of 21%; and 3) UCT can be improved with the clinical control of the disease. Indeed, the improvement was recorded in 62% of patients with ulnar nerve entrapment at the elbow.

Ulnar nerve compression may occur at the level of the elbow at different anatomic sites but the cubital tunnel is the most common site. It contains the ulnar nerve and is delimited by the cubital tunnel retinaculum which joins the medial epicondyle, the *olecranon*, and the *flexor*

Table 1 Results of clinical examination, NCS, and US in the diagnosis of UCT.

Acromegalic patients ($n=37$)	Clinical examination for UCT	NCS for UCT	US for UCT	Final diagnosis of UCT
Baseline	9/37	3/9	8/9	8/37
After 1 year	3/8	2/8	3/8	3/8

n, number; UCT, ulnar cubital tunnel syndrome; NCS, nerve conduction study; US, ultrasonography. Note that a negative NCS does not exclude the diagnosis of UCT if the clinical examination and the US signs of nerve entrapment are positive. One patient with a positive clinical examination received a diagnosis of CTS ('non-median' distribution of symptoms). In bold, patients with baseline diagnosis of UCT. Note that after 1 year UCT was recorded in only 3 patients.

Table 2 Results of the comparison between ulnar nerve CSA at the cubital tunnel in acromegalic patients and controls.

	Controls	Acromegaly	Acromegaly UCT	Acromegaly UCT 1 year	P
No.	50	37	8	3	
Age (years)	54.9±3.1	54.9±3.2	51.3±16.1	58.9±6.2	
F/M	25/25	18/19	5/3	2/1	
Disease duration (years)	—	5.1±2.6	3.7±2.9	4.4±2.3	0.328
GH levels (µg/l)	—	6.63±0.7	16±9.4	2.2±0.9	0.276
IGF1 levels (µg/l)	—	332.2±27.1	526±83.4	344±20.8	0.075
Nerve CSA (mm ²)	6.8±1.2	11.1±2.3*	16.7±2.9 [†]	12.2±3.1*	0.001* 0.047 [†]

UCT, ulnar cubital tunnel syndrome. Data are expressed in mean±s.d. for age, disease duration, and ulnar nerve cross-sectional area (CSA). GH and IGF1 values are expressed in mean±s.e.m. All groups versus controls: **P*<0.001; acromegalic patients with UCT versus acromegalic patients without UCT: [†]*P*<0.047. Note the reduction of GH and IGF1 values in acromegalic patients with UCT after 1 year (a good correlation has been evident between GH and IGF1 values in patients with UCT before and after a year: *r*=−0.88 and −0.45 respectively).

carpi radialis aponeurosis. It has been recently demonstrated that acromegalic neuropathy is represented by a diffuse nerve enlargement which may involve the peripheral nerves (3, 5). Since also the ulnar nerve resulted affected, in this study we tried to identify if a UCT was present in patients with a positive clinical examination. Indeed, UCT was recorded in 21% of patients. Moreover, we also evaluated the natural history of UCT in acromegalic patients referred to an endocrine unit. It is interesting to note that the prevalence of UCT was similar to the prevalence of CTS found by other authors (1). However, the adjunct of US to the clinical and NCS increases the overall sensitivity of the diagnosis, especially for UCT where NCS may be normal in mild cases (4, 15). We believe that this relatively high prevalence of UCT may be explained by the use of US which has never been employed in acromegaly. The multimodality approach

Figure 2 Short-axis US image of the ulnar nerve (dotted circle) at the cubital tunnel in three different subjects. (a) Normal ulnar nerve in a normal control, (b) slightly enlarged ulnar nerve in an asymptomatic acromegalic patient, (c) markedly enlarged ulnar nerve in a symptomatic ‘*de novo*’ acromegalic patient consistent with UCT, (d) reduction of ulnar nerve CSA in the same patient after 1-year therapy and symptoms resolution (SSA). O, *olecranon*; SSA, *somatostatin analogues*.

Figure 3 (a) Schematic of the arm and forearm where the two most common entrapment neuropathies occur in acromegalic patients. Ulnar nerve entrapment at the elbow (UCT) determines a swelling of the nerve proximally to the cubital tunnel (black arrow). Median nerve entrapment at the carpal tunnel is represented by an enlargement of the nerve (void black arrow). M, median nerve; U, ulnar nerve; H, humerus. (b) A photograph illustrates the different distribution of paresthesias in the hand of acromegalic patients. The first three fingers are affected by CTS, on the contrary the IV and V fingers are affected by UCT. Note that on the radial side of the IV finger an overlap between median and ulnar nerve symptoms is possible.

to UCT allowed US to differentiate UCT from mild CTS with a sensory disturbance involving the hands. UCT identification may prevent considerable discomfort and disability for the patient and, in late and unrecognized cases, the loss of function of the hand (4). Moreover, early recognition of an entrapment neuropathy is important to begin an appropriate conservative treatment to avoid a non 'risk-free' surgery (4).

Differential diagnosis from these two entrapment neuropathies is crucial due to the different therapeutic approaches. In fact, in CTS surgery is considered the treatment of choice, while in UCT conservative therapy including patient education has good outcomes (4). Other authors observed that almost 50% of patients with mild UCT who refused surgery reported an improvement at follow-up (16). Conservative therapy for UCT include patient education to avoid activities that reproduce symptoms such as repetitive elbow flexion or direct pressure to the medial epicondyle, splinting, and work environment modification (17). Unlike CTS, the response to UCT from steroid injections is limited, therefore steroids should be avoided in UCT (17). The fraction of patients (62%) in which we observed an improvement is higher than previously reported (16). It is possible that this phenomenon could be related to the control of acromegaly since four of them had a controlled disease after 1 year follow-up. Moreover, in the group who did not reported any clinical or US improvement, no controlled patients were present. In our series, UCT seems to be an early manifestation of the disease since it was present in three out of six *de novo* patients. However, a possible limitation of our study is the relatively small number of patients.

In conclusion our study reveals that sensory disturbances in acromegalic patients are not only due to median nerve entrapment at the carpal tunnel CTS but also to ulnar nerve entrapment at the level of the elbow UCT as shown in Fig. 3. In acromegalic patients, ulnar neuropathy can improve with the control of the disease and avoid surgical treatment. In acromegalic patients with acroparesthesias, physicians should consider UCT in the differential diagnosis with CTS due to the different management and therapeutic approaches.

Declaration of interest

Alberto Tagliafico, Eugenia Resmini, Raffaella Nizzo, Lorenzo E. Derchi, Francesco Minuto, Massimo Giusti, Carlo Martinoli, Diego Ferone, have nothing to declare.

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