The pathology of 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 one 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 hypotiroidism with clinical examination, nerve conduction studies (NCS) and high-resolution ultrasound (US). A control group was made by 50 volunteers. Local ethic 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 one year.

Results: In 8/37 patients a diagnosis of UCT was made at the beginning of the study reflecting a prevalence of 21%. After one year 5/8 (62.5%) patients reported clinical and NCS improvements and evident US reduction of nerve CSA (16.7±2.9 mm² vs 12.2±3.1 mm²; p<0.001). In 3/8 (37.5%) patients the UCT was unchanged. Ulnar nerve CSA was significantly increased in acromegalic patients with UCT (16.7±2.9 mm² vs 11.1±2.3 mm²; 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 tunnel syndrome and carpal tunnel syndrome in acromegaly.
Introduction

Carpal tunnel syndrome (CTS) is a common complication of acromegaly occurring in 20-64% of patients at the 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 MRI that the predominate pathologic mechanism of median neuropathy in acromegaly seems 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 has been given to ulnar nerve entrapment at the elbow which may determine altered sensation in the little and ring finger and, in late stages, wasting of the small muscles of the hand and of the ulnar-side forearm (4). UCT if often misdiagnosed and the adjunct of 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 asses UCT in acromegalic patients at baseline and after one year treatment.
Material and Methods

Patients
We prospectively evaluated 37 acromegalic patients (18 f and 19 m, age range, 18-79 yrs; disease duration range, 1-15 yrs) and 50 healthy age-, sex and BMI-matched controls with no history of polyneuropathy, acute trauma at the elbow, alcohol abuse, vitamin B12 deficiency, diabetes or hypothyroidism with clinical examination, 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 to transsphenoidal neurosurgery, (10 of these were also treated with somatostatin analogues), 9 underwent primary medical therapy with somatostatin analogues, the remaining one underwent radiotherapy and medical therapy with octreotide. Disease activity was evaluated by GH measurement during OGTT and the basal value of IGF-I, and the patients were subdivided in 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 IGF-I values was noted. The study was approved by the local ethical committee and written informed consent was obtained from all patients and controls.

Clinical examination
During physical examination 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 (NCV) 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 Electrodagnostic 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 increases the sensitivity of clinical examination and electrodiagnostic tests (10), we evaluated the ulnar nerve with a broadband (17-5MHz) linear array transducer. The adjunct of ultrasound 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 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 an area of 7.5 mm² (12). Patients with a diagnosis of UCT at the beginning of the study were re-evaluated after one year.

**Laboratory assays**
Circulating GH and IGF-I levels were determined as previously reported (13).

**Statistical analysis**
Statistical analysis was performed using SPSS 11.0 software. 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 one year. P values<0.05 were considered significant.
Results

Clinical examination

A total of 37 patients have been evaluated. At the beginning of the study 13/37 acromegalic patients were asymptomatic, 15/37 patients referred sensory disturbances related to the median nerve and so these patients were excluded. The remaining 9/37 patients (3 de novo, 2 with uncontrolled acromegaly, 1 partially controlled and 3 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 1/9 of them. 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 one year, the 8 patients with sensory disturbances in the territory of the ulnar nerve, and without CTS, have been evaluated again: 5/8 patients (1 uncontrolled and 4 controlled, 2 of them de novo at the beginning) reported clinical improvement of the sensory abnormalities while 3/8 patients (2 uncontrolled, 1 de novo at the beginning and 1 partially controlled) did not.

Neurophysiological examination

Patients identified at physical examination with possible ulnar neuropathy underwent NCS to confirm clinical data. In the n=3/8 patients with weakness or atrophy NCS confirmed the diagnosis of UCT, while in 5/8 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 one year n=6/8 patients had a normal NCS while n=2/8 patients had no changes in the electrophysiological examination.

In 14/15 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.

Ultrasoundography

Nine patients with symptoms related to the ulnar nerve were evaluated at the beginning of the study and after one year. Nerve CSA was over the cut-off value in all of these 9 patients. In 8 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 loss of the fascicular pattern proximal to the cubital tunnel. The remaining one had an US signs of nerve compression consistent with a CTS. After one year in the 5 patients (62%) who reported a clinical improvement there was an evident reduction of the ulnar nerve CSA. In 3 patient without a 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 8 patients (Table 1a). One patient with sensory disturbances on the hand as a whole was considered as a CTS with a “glove” distribution of paresthesias (12), and was excluded. We considered also the 5 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 electrodagnostic 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 Table 1b, 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%; 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 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 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, 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 outcome (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 4 of them had a controlled disease after one 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 3 out of 6 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.
References


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Legends to the figure

**FIG. 1:** Normal longitudinal 17-5 MHz US of the ulnar nerve at the cubital tunnel in a normal subject in a. In 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).

**FIG. 2:** Short-axis US image of the ulnar nerve (dotted circle) at the cubital tunnel in 3 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 one year therapy and symptoms resolution (SSA).

O: olecranon; SSA: somatostatin analogues

**FIG. 3:** Schematic drawing a 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. In 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 finger are affected by UCT. Note the on the radial side of the IV finger an overlap between median and ulnar nerve symptoms is possible.
Table 1. a. Results of clinical examination, NCS and US in the diagnosis of UCT, and b. Results of the comparison between ulnar nerve CSA at the cubital tunnel in acromegalic patients and controls.

<table>
<thead>
<tr>
<th>Acromegalic Patients (n=37)</th>
<th>Clinical examination for UCT</th>
<th>NCS for UCT</th>
<th>US for UCT</th>
<th>Final diagnosis of UCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>9/37</td>
<td>3/9</td>
<td>8/9</td>
<td>8/37</td>
</tr>
<tr>
<td>After 1 year</td>
<td>3/8</td>
<td>2/8</td>
<td>3/8</td>
<td>3/8</td>
</tr>
</tbody>
</table>

Legend: n, number; UCT, ulnar cubital tunnel syndrome; NCS, nerve conduction study; US, ultrasonography. Note that a negative NCS do 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>
<thead>
<tr>
<th>controls</th>
<th>acromegaly</th>
<th>acromegaly with UCT</th>
<th>acromegaly with UCT 1 yr</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>50</td>
<td>37</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>54.9±3.1</td>
<td>54.9±3.2</td>
<td>51.3±16.1</td>
<td>58.9±6.2</td>
</tr>
<tr>
<td>F/M</td>
<td>25/25</td>
<td>18/19</td>
<td>5/3</td>
<td>2/1</td>
</tr>
<tr>
<td>Disease duration (yrs)</td>
<td>-</td>
<td>5.1±2.6</td>
<td>3.7±2.9</td>
<td>4.4±2.3</td>
</tr>
<tr>
<td>GH levels (µg/l)</td>
<td>-</td>
<td>6.63±0.7</td>
<td>16±9.4</td>
<td>2.2±0.9</td>
</tr>
<tr>
<td>IGF-I levels (µg/l)</td>
<td>-</td>
<td>332.2±27.1</td>
<td>526±83.4</td>
<td>344±20.8</td>
</tr>
<tr>
<td>Nerve CSA (mm²)</td>
<td>6.8±1.2</td>
<td>11.1±2.3*</td>
<td>16.7±2.9**</td>
<td>12.2±3.1*</td>
</tr>
</tbody>
</table>

Legend: UCT, ulnar cubital tunnel syndrome. Data are expressed in mean ± SD for age, disease duration and ulnar nerve cross-sectional area (CSA). GH and IGF-I values are expressed in mean ± SEM. All groups vs. controls: *p<0.001; acromegalic patients with UCT vs. acromegalic patients without UCT: **p<0.047. Note the reduction of GH and IGF-I values in acromegalic patients with UCT after one year (a good correlation has been evident between GH and IGF-I values in patients with UCT before and after a year: r=-0.88 and -0.45 respectively).