Ultrasound of peripheral nerves in acromegaly: Changes at 1-year follow-up

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Purpose

Median neuropathy at the level of the carpal tunnel is documented in acromegaly [1-3], whereas only few studies deal with involvement of nerves other than the median, such as the ulnar nerve, to explain sensory disturbances that typically affect the hands of patients with acromegaly [4,5].

In the last few years, ultrasonography (US) has been increasingly used for the non-invasive assessment of a wide range of nerve diseases in the extremities, such as entrapment syndromes, traumatic injuries and tumours [6]. It has also proved able to characterize hereditary neuropathies and metabolic disorders, with advantages including a higher spatial resolution than surface-coiled Mr imaging, and the ability to follow long nerve segments in a single study [7,8].

Our recent study has suggested that nerves of acromegalic patients are significantly enlarged when compared with those of normal subjects [9]. In contrast to focal neuropathies, the pattern of nerve enlargement is diffuse and tends to be uniform throughout the upper extremity [9]. This finding seems to represent an intrinsic feature of the disease that is related to clinical control, disease duration, and IGF-I levels. Ultrasonographers should become familiar with these abnormalities to avoid false positives of carpal tunnel syndrome when examining acromegalic patients. In addition, care should be taken if a diffuse enlargement of more than one nerve throughout the limbs and extremities without abnormalities in the fascicular echotexture is recorded. Indeed, these US findings should prompt suspicion of the presence of acromegaly in previously undiagnosed patients undergoing this investigation.

The aim of the present study was to depict the main features and evolution of nerves in these patients, with high-resolution US, after 1 year from the first evaluation, and to explore the possible correlations between clinical parameters and disease control.
Methods and Materials

Patients

We prospectively examined 34 consecutive patients with acromegaly, 18 females and 16 males, age range 18-79 year (54.9 ± 3.20 year, mean ± SEM), body mass index (BMI) 25.2 ± 0.90 mean ± SEM, disease duration range 1-15 years (5.1 ± 0.85 mean ± SEM) and 34 healthy volunteers matched for sex, age and BMI, 18 females and 16 males, age range 23-79 year (41.9 ± 4.62 mean ± SEM), BMI (25.1 ± 0.75 mean ± SEM), which served as a control group.

The diagnosis of acromegaly was based on established criteria: acromegaly is identified when nadir GH levels after OGTT is > 1 µg/l and IGF-I levels are above normal range for age and sex [10].

No patients with diabetes mellitus were recruited in this study to avoid possible interference with diabetic neuropathy [11]. Similarly, patients with hypothyroidism were not included [12].

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

Patients were examined at baseline and after 1 year, and during this year a number of patients changed their clinical status due to the therapies.

The six newly diagnosed patients at baseline underwent neurosurgery after primary medical therapy with somatostatin analogues. Four of six were cured after surgery, whereas the remaining two underwent postsurgery somatostatin analogue adjuvant therapy. In this group the first US (baseline) was made at the diagnosis, without any therapy. The second US (follow-up) was made after neurosurgery and after 1 year from the previous one.

The seven patients already on primary medical therapy with somatostatin analogues at baseline continued their treatment. In this group the first US (baseline) was made at the beginning of the study and the second US (follow-up) was made after 1 year.

Among the 20 patients who had undergone trans-sphenoidal neurosurgery before study entry, 9 were cured after surgery, 11 received adjuvant medical therapy and continued their treatment with somatostatin analogues, whereas 2 of 11 (spontaneously) discontinued the therapy. In this group, the first US (baseline) was made at the beginning of the study and the second US (follow-up) was made after 1 year. The two patients who discontinued the medical therapy were on therapy at the baseline US, but off medical therapy at the follow-up scan. The others remained on the same therapy during the year.
The only patient who had previously undergone radiotherapy continued medical therapy with octreotide during the year of followup. In this patient the first US (baseline) was made at the beginning of the study and the second US (follow up) was made after 1 year, when on the same therapy.

First we performed a time per group analysis, taking all together the nerve cross-sectional area (CSA) of the 34 patients, compared at baseline and after 1 year of follow up. Therefore, we divided the cohort of patients in four subgroups for better understanding what happened in the different clinical situations.

Disease activity was evaluated by GH measurement during an oral glucose tolerance test, and basal value of IGF-I, calculated as standard deviation scores (SDS) [10,13]. Disease control has been defined in three 'grades' as follows: Grade 1, controlled (GH after glucose # 1 µg/l and IGF-I < 2 SDS for age); Grade 2, partially controlled (either GH or IGF in the controlled range); Grade 3, uncontrolled (GH > 1 and IGF-I # 2 SDS).

Patients were subdivided in four subgroups according to the control of the disease observed at first examination and at follow-up:

(1) 'improved', n = 12 (patients who shifted from grade 3 to 2 or from grade 3 to 1, or from grade 2 to 1 at follow-up)

(2) 'always controlled', n = 12; (patients who were grade 1 at both first examination and follow-up)

(3) 'always uncontrolled', n = 6 (patients who were grade 3 at both first examination and follow-up)

(4) 'worsened', n = 4 (patients who shifted from grade 1 to 2 or 3 or from grade 2 to 3 at follow-up).

Patients who were in grade 2 (partially controlled) at baseline became grade 1 or grade 3 at follow-up, but did not remain in grade 2.

Sensory disturbances in the territory of median and ulnar nerve were also recorded during clinical examination, as previously reported [9].

The patients were also classified according to whether they were receiving medical treatment with somatostatin analogues at the beginning of the study, treated (n = 18), and untreated (n = 16).

**Ultrasound studies**
US examination of the median and ulnar nerves was performed with a digital scanner equipped with a broadband (frequency band, 17-5 MHz) linear array transducer, as previously reported [9]. Interpretation of the US images was based on measurement of the nerve CSA. Briefly, in each study, the median nerve was examined at the level of the mid-forearm (MN-f) and carpal tunnel (MN-ct), while the ulnar nerve was assessed at the mid-forearm (UN-f) and at distal arm (UN-a). A total of 272 CSAs of nerves in patients with acromegaly were compared with controls, and also the follow up CSAs were compared with the baseline values in each individual patient with acromegaly (Fig. 1). All US studies were performed by the same examiner (A.T.), who was a radiologist experienced in musculoskeletal US, to avoid interobserver variability, using the same instrument of the first examination. Nerve CSA of each patient and control was normalized for the BMI. Statistical analysis was performed on normalized nerve CSAs.

**Laboratory assays**

Serum GH levels were determined by means of a chemioluminescent ICMA assay. The analytical sensitivity of this assay was 0·01 µg/l, and the accuracy was < 7% in the standard curve range; the standard curve was calibrated against WHO 1st IRP 80/505 (1 mg = 2.6 IU). All these data have been validated in our laboratory.

IGF-I was measured by a radioimmunoassay. The sensitivity of the assay was 150 µg/l; the intra- and interassay coefficients of variation were 6% and 7.5%, respectively. In order to avoid interferences due to binding proteins, single plasma EDTA samples were treated with ethanol, according to Daughaday et al. [14]. IGF-I was measured in basal conditions and it was reported as age-based SDS, calculated on the basis of data obtained from over 4000 normal subjects of both sexes, from 0 to 100 years, grouped into decades of age. Moreover, to estimate IGF-I modifications within the interval between the first evaluation and follow-up, % values [(follow-up-baseline) × 100/baseline] were calculated.

**Statistical analysis**

Comparison of radiological parameters in acromegalic patients at first examination and at follow-up was made by Student's *t* -test for paired data, whereas comparison between patients with acromegaly and controls was made by Student's *t* -test for unpaired data. Correlation between nerve CSAs with other parameters, was made by the Pearson's test. ANOVA for repeated measures, were used where appropriate.

Values were expressed as mean ± SEM and probability (*P*) values < 0.05 were considered statistically significant.
Fig. 0: Ultrasnographic comparison of nerves of acromegalic patients (left) and controls (right) at the four points of measurement. The nerve appears enlarged at the four points of sampling. Note the position of the calipers used to calculate the long and short axis of the nerve.

Results

After 1 year follow-up we found 25 controlled patients, whereas at baseline there were only 14. In particular, among the six naïve patients, five were controlled, whereas one was still uncontrolled at follow-up. Hormonal changes in the four groups are summarized in Table 1 (Fig.1)

We performed a time per group analysis, taking together all the nerve CSA of the 34 patients, compared at baseline and after 1 year follow-up. We found that the median nerve at the mid-forearm (MN-f), the ulnar nerve at the mid-forearm (UN-f) and at distal arm (UN-a) were significantly reduced after 1 year follow-up (\( P < 0.001, P < 0.008, P < 0.012 \), respectively).

Comparison between nerves' ultrasound parameters at first evaluation and at 1 year follow-up

In the 'improved' group, there was a significant reduction of MN-f and UN-a (\( P = 0.02 \) and 0.002, respectively). However, UN-a, UN-f, MN-f, MN-ct were still significantly higher compared with controls (\( P < 0.001 \)).

In the 'always controlled' group no statistically significant differences were found at the single sites of measurements, although UN-a and UN-f showed decreases which were near to significance (\( P = 0.052 \) and \( P = 0.060 \), respectively).

In the 'always uncontrolled' group and in the 'worsened' group no statistically significant differences in the ultrasound parameters were recorded.

Overall, CSAs of nerves in the four groups of patients were all significantly larger compared with controls (\( P < 0.001 \)).

According to medical treatment both groups (treated and untreated) had statistical significantly enlarged nerves at all the four sites of sampling compared to the control group (\( P < 0.001 \)), but no differences were observed between baseline and follow-up (Fig. 2)

Correlations between radiological parameters and GH and IGF-I levels
As expected, a significant correlation was found between GH and IGF-I (absolute values $r = 0.68$, SDS $r = 0.37$), whereas no correlation was found between GH levels and any radiological parameter.

IGF-I SDS was positively correlated with MN-ct ($r = 0.28$, $P < 0.05$), UN-a ($r = 0.36$, $P < 0.01$).

IGF-I percentage # values were significantly correlated only with UN-a ($r = 0.37$, $P < 0.05$) (Fig. 3).

**Sensory disturbances in the territory of median and ulnar nerve**

In *improved* (12 patients), symptoms disappeared in seven patients. Conversely, symptoms appeared in one previously asymptomatic patient, whereas the remaining four were unchanged (three with no symptoms and one with symptoms at both first evaluation and follow-up).

In *always controlled* (12 patients), symptoms disappeared in two patients at follow-up. The remaining patients were unchanged (eight asymptomatic and two symptomatic).

In *always uncontrolled* (6 patients), symptoms disappeared in two patients. Conversely, symptoms appeared in two previously asymptomatic patients, whereas the remaining two were unchanged (one with no symptoms and one with symptoms at both first evaluation and follow-up).

In *worsened* (4 patients), symptoms appeared in one previously asymptomatic patient, whereas the remaining three were unchanged (three with symptoms at both first evaluation and follow-up).
### Table 1. Hormonal changes in the four groups of acromegalic patients

<table>
<thead>
<tr>
<th>Group</th>
<th>First evaluation</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GH nadir</td>
<td></td>
</tr>
<tr>
<td>‘Improved’ (n = 12)</td>
<td>5·01 ± 1·48</td>
<td>0·81 ± 0·14**</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>4·95 ± 1·07</td>
<td>0·83 ± 0·21**</td>
</tr>
<tr>
<td>‘Always controlled’ (n = 12)</td>
<td>0·34 ± 0·11</td>
<td>0·62 ± 0·09</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>0·94 ± 0·20</td>
<td>0·68 ± 0·11</td>
</tr>
<tr>
<td>‘Always uncontrolled’ (n = 6)</td>
<td>18·19 ± 14·7</td>
<td>5·45 ± 1·98***</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>4·56 ± 0·99</td>
<td>3·38 ± 0·48*</td>
</tr>
<tr>
<td>‘Worsened’ (n = 4)</td>
<td>0·87 ± 0·26</td>
<td>3·41 ± 1·40</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>1·04 ± 0·41</td>
<td>1·37 ± 0·65</td>
</tr>
</tbody>
</table>

Values in the table are expressed as mean ± SEM.

*P < 0·05; **P < 0·01; ***P < 0·001.

**Fig. 0:** Table 1. Hormonal changes in the four groups of acromegalic patients

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<table>
<thead>
<tr>
<th>Group</th>
<th>First evaluation</th>
<th>Follow-up</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Improved’ ((n = 12))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MN-Ct</td>
<td>15.8 ± 0.90</td>
<td>14.6 ± 1.55</td>
<td>7.5 ± 0.49</td>
</tr>
<tr>
<td>MN-f</td>
<td>11.0 ± 0.75</td>
<td>9.1 ± 0.54*</td>
<td>5.6 ± 0.31</td>
</tr>
<tr>
<td>UN-a</td>
<td>14.6 ± 0.96</td>
<td>10.1 ± 0.59**</td>
<td>6.6 ± 0.88</td>
</tr>
<tr>
<td>UN-f</td>
<td>8.9 ± 0.57</td>
<td>8.5 ± 0.57</td>
<td>5.5 ± 0.36</td>
</tr>
<tr>
<td>‘Always controlled’ ((n = 12))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MN-Ct</td>
<td>15.1 ± 1.06</td>
<td>14.9 ± 0.88</td>
<td>7.5 ± 0.49</td>
</tr>
<tr>
<td>MN-f</td>
<td>10.3 ± 0.65</td>
<td>9.6 ± 0.70</td>
<td>5.6 ± 0.31</td>
</tr>
<tr>
<td>UN-a</td>
<td>13.6 ± 1.03</td>
<td>12.6 ± 1.14</td>
<td>6.6 ± 0.88</td>
</tr>
<tr>
<td>UN-f</td>
<td>10.3 ± 0.65</td>
<td>9.9 ± 0.85</td>
<td>5.5 ± 0.36</td>
</tr>
<tr>
<td>‘Always uncontrolled’ ((n = 6))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MN-Ct</td>
<td>18.3 ± 1.29</td>
<td>15.2 ± 0.67</td>
<td>7.5 ± 0.49</td>
</tr>
<tr>
<td>MN-f</td>
<td>8.5 ± 0.34</td>
<td>7.0 ± 0.31</td>
<td>5.6 ± 0.31</td>
</tr>
<tr>
<td>UN-a</td>
<td>12.5 ± 0.93</td>
<td>9.3 ± 0.44</td>
<td>6.6 ± 0.88</td>
</tr>
<tr>
<td>UN-f</td>
<td>10.3 ± 1.16</td>
<td>10.8 ± 0.72</td>
<td>5.5 ± 0.36</td>
</tr>
<tr>
<td>‘Worsened’ ((n = 4))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MN-Ct</td>
<td>15.8 ± 1.06</td>
<td>16.5 ± 1.37</td>
<td>7.5 ± 0.49</td>
</tr>
<tr>
<td>MN-f</td>
<td>11.6 ± 0.83</td>
<td>9.5 ± 0.75</td>
<td>5.6 ± 0.31</td>
</tr>
<tr>
<td>UN-a</td>
<td>11.7 ± 1.03</td>
<td>12.3 ± 0.77</td>
<td>6.6 ± 0.88</td>
</tr>
<tr>
<td>UN-f</td>
<td>8.7 ± 0.67</td>
<td>7.8 ± 0.62</td>
<td>5.5 ± 0.36</td>
</tr>
</tbody>
</table>

Values in the table are expressed in mm² as Mean ± SEM.
*\(P < 0.05\); **\(P < 0.01\) vs. first evaluation.

The median nerve was examined at the mid-forearm (MN-f) and at the carpal tunnel (MN-ct) level, while the ulnar nerve at the mid-forearm (UN-f) and at distal arm (UN-a).

**Fig. 0:** Nerve cross-sectional area (CSA) of median and ulnar nerves in the four groups of patients with acromegaly at first evaluation and at 1 year follow-up

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Fig. 0: Correlation between #% IGF-I and ultrasound of ulnar nerve at distal arm (UN-a) variations in single subjects with acromegaly (n = 34).

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Conclusion

Peripheral neuropathy is a common manifestation of acromegaly, first reported in 1891 [15]. In this disorder, the nerve involvement is multifaceted and may be recognized with difficulty, especially in patients with systemic complications [16].

From the pathophysiological point of view, there is no consensus in literature to the explanation of nerve involvement in acromegaly. Indeed, it may be secondary to intrinsic factors, including histopathological changes and intraneural oedema, or extrinsic problems related to the fact that nerves cross-joints passing through narrow passageways, the osteofibrous tunnels, within which they may undergo compression. US allowed an accurate and reliable depiction of both median and ulnar nerves based on established criteria[6]. On short-axis planes, nerves exhibited a well-defined honeycombing appearance made up of multiple rounded hypoechoic fascicles embedded in the hyperechoic epineurium.

In a previous pilot study we examined nerves in patients with acromegaly using high-resolution US to assess the possible value of imaging in this heterogeneous and clinically challenging group [9]. We selected the median and the ulnar nerves, because acromegalic patients most often present with symptoms suggestive of pathology involving these nerves. Both nerves were examined at different levels in the arm and the forearm, including the carpal tunnel and also areas outside osteofibrous tunnels, to avoid any interference on nerve morphology induced by tunnel shape or by possible entrapment.

Whatever the sampling site or nerve examined, acromegalic nerves showed a significantly larger CSAs compared with the corresponding nerves of normal subjects. The nerve enlargement was diffuse throughout the upper extremity, indicating a disease-related process that was basically unrelated to entrapment syndromes. In addition, the fascicular echotexture was always preserved a figure that may be lost in focal neuropathies. Other peripheral neuropathies have a distinct clinical picture, different from that we found in patients with acromegaly [9]. Based on these latter new findings, the characteristics of nerve enlargement in acromegaly seem to reflect a specific disease-related process rather than the result of a compressive neuropathy.

In the present study we found that nerves’ CSA decreased after 1 year follow-up in patients with acromegaly. However, the median nerve reduction was significantly evident only at the forearm (MN-f), but not at the carpal tunnel level, possibly because at this level other confounding factors, such as flexor tenosinovitis or carpal tunnel syndrome, may complicate clinical setting. In this group nerve CSAs although reduced, did not normalize. Concerning the reduction of ulnar nerve CSA at the level of the arm, we have to note that this data may be enhanced also by the concomitant presence of cubital tunnel syndrome, which can improve in 62% of cases with disease control [17].
However, as the group of 'always controlled' patients also showed a tendency to reduction, but not normalization, of nerve CSA, it seems that a progressive improvement may still occur during the constant control of the disease activity. This suggests that the reduction of nerve size is very slow and/or only partially reversible. In 'worsened' patients no significant modifications of nerve CSAs were observed, suggesting that nerve enlargement occurs in the early stages of the disease and progresses very slowly. However we have to acknowledge that a group of four patients could be difficult to analyse from the statistical point of view due to the low number of patients in each group. The division in the four subgroups could be useful for better understanding what happened in the different clinical conditions.

Concerning treatment with somatostatin analogues, we did not observe any difference between baseline and follow-up, therefore we infer that treatment with somatostatin analogues does not influence the volume of peripheral nerves. As far as the hormonal state is concerned, a positive correlation between nerve CSAs and IGF-I, but not GH, was found, suggesting that nerve swelling in acromegaly might be a direct effect of IGF-I. This is in line with data in the literature showing that IGF-I directly influence nervous tissue [18,19]. Indeed, IGF-I affects multiple layers of the regenerative response in peripheral nerve regeneration. The elements of peripheral nerve regeneration comprise a complex combination of events: nerve growth, muscle satellite cell proliferation/differentiation, and vessel growth. IGF-I participates at different levels in this setting: as a neurotrophic factor, it is known to promote nerve elongation and branching, whereas, as a myogenic factor, IGF-I promotes satellite cell proliferation, differentiation and muscle hypertrophy. Moreover, as an angiogenic factor, IGF-I is known to promote angiogenesis in regenerating skeletal muscle by activating VEGF and VEGF receptors [19]. Finally, in vivo IGF-I, in the presence of other permissive factors, can promote myelination both in the central nervous system and in peripheral nerves [20].

Recent data suggest reciprocal influences of neurones on gene expression in muscle and of muscle on age-related neurodegeneration. The role of nerves in regulating the trophic actions of IGF-I, and other neurotrophic factors, is considered a novel way of influence on the effects of ageing on the neuromuscular junction [21].

We have also previously demonstrated that there is a positive correlation between nerve CSA and disease duration [9]. Interestingly, in the present study, among the six naive patients, five, included in the 'improved' group, displayed a reduction in CSA much more evident than the other of the same group. These patients have a shorter disease duration than the others. This finding supports the hypothesis that both disease duration and clinical control of the disease affect the nerve picture in acromegaly. Our findings suggest that nerve enlargement is probably an early event and keeps slowly progressing during the years of the disease, and may become, at least in part, irreversible. By consequence, short disease duration (early diagnosis) and rapid control maximizes the probability of regression. Ultrasonographers should be aware that finding a nerve enlargement may suggest the presence of acromegaly disease requiring referral to an endocrinologist.
In conclusion, our data suggest that treatment of acromegaly with standard protocols produces a reversal of the nerve enlargement, which is proportional to the degree of disease control, particularly to IGF-I levels. However, even if complete control of disease is achieved for long time, the nerve dimensions are larger than normal subjects. We suggest that early diagnosis and prompt control might enable nerve normalization and reduce clinical manifestation of acromegalic neuropathy.
References


