Case Report

Role of Biphosphonates and Lymphatic Drainage Type
Leduc in the Complex Regional Pain Syndrome
(Shoulder–Hand Syndrome)

Andrea Santamato, MD,* Maurizio Ranieri, MD, PhD,† Francesco Panza, MD, PhD,‡
Vincenzo Solfrizzi, MD, PhD,‡ Vincenza Frisardi, MD,‡ Ida Stolfa, MD,† Marisa Megna, MD,†
and Pietro Fiore, MD*

*Department of Physical Medicine and Rehabilitation, University of Foggia, Foggia; †Department of Neurological and
Psychiatric Sciences; ‡Department of Geriatrics, Center for Aging Brain, Memory Unit, University of Bari, Bari, Italy

A B S T R A C T

Background. Complex regional pain syndrome (CRPS) is a clinical entity that has been termed in numerous ways in the last years. Clinically, CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings.

Design. Case report.

Setting. University Medical Center.

Patients. In this report, we described the case of a 68-year-old hemiplegic female affected by cerebrovascular accident that presented a clinical case of CRPS shoulder–hand syndrome (CRPS-SHS) at the right hand after a hemorrhagic stroke.

Interventions. This report evaluated the effects of biphosphonates and lymphatic drainage type Leduc in CRPS-SHS.

Outcome Measures. The pain level of the patients was measured with the visual analog scale. A scoring system for the clinical severity of CRPS-SHS, laboratory tests, and X-ray films were also performed.

Results. We reported in this patient a great improvement of pain and edema of the right hand, with a significant reduction of bone demineralization.

Conclusions. This combined treatment may be a viable alternative for this syndrome; however, further investigation is needed to determine its reproducibility in large case series.

Key Words. Complex Regional Pain Syndrome; Reflex Sympathetic Dystrophy Syndrome; Shoulder–Hand Syndrome; Stroke; Biphosphonates; Lymphatic Drainage

Introduction

Complex regional pain syndrome (CRPS) is the currently accepted term for a clinical entity that has been termed in numerous ways in the last years: reflex sympathetic dystrophy syndrome (RSDS), causalgia, algodystrophy, Sudeck's atrophy, shoulder–hand syndrome (SHS),
The syndrome, which was first described in 1864 by Sir Silas Weir Mitchell [5], is characterized by persistent neuropathic pain of great intensity, swelling, limited range of motion with associated signs of vasomotor instability, trophic skin changes, and patchy bone demineralization of one extremity after a trauma. The initiating trauma affected primarily the extremity, but can also be a central lesion (e.g, spinal cord injury, stroke). Distal parts of upper extremity, the hand, and the wrist typically are affected by this pathology. In 35% of the CRPS patients, no precipitating event can be identified.

A consensus workshop, held in 1994 in Orlando, Florida, introduced the purely descriptive term “complex regional pain syndrome” [1], with the new name and diagnostic criteria codified by the International Association for the Study of Pain (IASP) task force on taxonomy [6]. Two types of CRPS have been recognized: CRPS type I (CRPS-I), corresponds to RSDS and occurs without a definable nerve lesion, and CRPS type II (CRPS-II), formerly called causalgia, refers to cases where a definable nerve lesion is present [1,4]. The incidence of CRPS-I was obviously higher than CRPS-II [1,3]. Despite a significant overlap in clinical symptomatology, there was one important difference between these two syndromes: the presence of an apparent peripheral nerve [7]. The syndrome was considered to develop in three consecutive phases: I, acute; II, dystrophic; and III, atrophic [8]. However, in the recent consensus workshop held in Budapest, Hungary, in 2003, there was no validation that the syndrome evolved in clinical stages or that early treatment was more beneficial than later [4,9]. In fact, three relatively homogeneous CRPS subtypes based on similarity of sign/symptom patterns were identified: 1) a relatively limited syndrome with vasomotor signs predominating; 2) a relatively limited syndrome with neuropathic pain/sensory abnormalities predominating; and 3) a florid CRPS syndrome similar to “classic RSDS” descriptions [4,10]. The resulting CRPS subgroups did not differ significantly regarding pain duration, as might be expected in a sequential staging model. Moreover, differences in clinical presentation between subgroups 1 and 2 might reflect the differing diagnoses of CRPS type I and II, respectively [4]. At present, pathophysiology of this disorder is unknown.

The prevalence of CRPS after cerebral damage is reported in literature as varying from 12.5% to 27% [11]. Besides classical clinical form, affecting distal and proximal part of extremity, the incomplete forms confined only to one of these parts may exist [11]. CRPS of the upper arm after stroke is still frequently known as SHS. The incidence of CRPS-SHS after cerebral damage had variable estimates: from 1.5% to 70% [11–13]. The present report described the development and the treatment of CRPS-SHS in a patient affected by hemorrhagic stroke.

Case Report

We described in this report the case of a 68-year-old hemiplegic female affected by hemorrhagic stroke with an approximately 2 months history of pain in the right hand, treated between 2006 and 2007 at the Department of Neurological and Psychiatric Sciences, University of Bari, Bari, Italy. After a cerebrovascular hemorrhagic accident, the patient presented a clinical picture characterized by hemiplegia at the right shoulder, wrist, and hand. In particular, the hand was plegic with flexion of fingers and wrist without any movement. Eight weeks after the hemorrhagic stroke, the condition started with pain, hyperalgesia, swelling, redness, and abnormal sudomotor activity in the right hand. According to the consensus workshop held in Budapest in August 2003, the diagnosis of CRPS was based on the proposed clinical diagnostic criteria [9] (Table 1). Initially, the signs and symptoms

![Table 1](https://example.com/table1.png)

For research purposes, diagnostic decision rules should be at least one symptom in all four symptom categories and at least one sign (observed at evaluation) in two or more sign categories.
symptoms were attributed to excessive rehabilitation, however, when cessation of exercises and anti-inflammatory treatment failed to improve the symptomatology, the diagnosis of CRPS-SHS was suspected.

The pain level of the patients was measured with visual analog scale (VAS). The VAS is used to measure pain: 10 cm horizontal axis between a left end point of “no back pain” and a right end point of “worst pain ever.” The distance was measured and pain was recorded on a 10-point scale [14]. In particular, VAS was 8/10 before combined treatment; at 1 month follow-up after the beginning of combined treatment, pain level was: VAS = 6/10; at 2 months follow-up, pain level was: VAS = 3/10. Furthermore, a scoring system for the clinical severity of CRPS-SHS was performed [15]. With this scale, patients with a total score of 4 or more were considered to have CRPS-SHS. This was assumed, empirically, to be the minimum score required to make this diagnosis. The maximum total score of 10 indicated the worst degree of the condition [15]. In this patient, laboratory tests were performed and it was found that urinary hydroxyproline, and serum alkaline phosphatase were slightly increased, and serum calcium was slightly reduced (Table 2). Furthermore, X-ray films were performed for the clinical-radiographic monitoring of possible bone abnormalities at the right hand, revealing mild osteopenia with patchy bone demineralization within fingers’ joints (Figure 1A). The patient was treated with intramuscular administration of 200 mg daily of disodium clodronate for 15 days. After this period, an intramuscular administration of 100 mg weekly of disodium clodronate was performed for 6 months.

Ten days after the beginning of treatment, when pain was reduced, the patient was undertaken to lymphatic drainage type Leduc [16] daily for 5 days/week, and subsequently at alternate days for 2 months. This is a particular method that consists on a combination of different therapies: manual lymphatic drainage associated with intermittent sequential pressotherapy with a very low intensity and multilayer bandages [16]. After the lymphatic drainage, the patient was managed with a static progressive finger extension orthosis. The orthosis was worn in full extension at night and for approximately 6 hours during the day.

Six months after starting therapy, the patient reported a regression of most signs and symptoms with also a modification of laboratory evaluations. In fact, the scoring system for the assessment of clinical severity of CRPS-SHS was 8.0/10 points before treatment, and 4.5/10 points after 6 months of combined treatment with biphosphonates and lymphatic drainage type Leduc (Table 3). Furthermore, laboratory evaluations after 6 months of combined treatment showed a reduction of urinary hydroxyproline, and serum alkaline phosphatase, and an increase of serum calcium (Table 2). Moreover, a reduction of edema of the right hand was found. The evaluation was done measuring 5 cm proximately to the radial styloid process, where edema was reduced of about 13.7 mm, and 10 cm distally to the radial styloid

<table>
<thead>
<tr>
<th>Laboratory evaluations</th>
<th>Before treatment</th>
<th>After 6 months treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium (8.5–10 mg/dL)</td>
<td>5.5</td>
<td>8.0</td>
</tr>
<tr>
<td>Urinary calcium (100–300 mg/24 hours)</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>Serum phosphate (2.5–4.8 mg/dL)</td>
<td>2.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Urinary phosphate (100–400 mg/24 hours)</td>
<td>288</td>
<td>256</td>
</tr>
<tr>
<td>Total serum alkaline phosphatase (30–170 UI/dL)</td>
<td>205</td>
<td>184</td>
</tr>
<tr>
<td>Total urinary hydroxyproline (6–22 mg/24 hours)</td>
<td>40</td>
<td>33</td>
</tr>
</tbody>
</table>

The units and range of normal values of biochemical variables are indicated.

Figure 1 X-ray films of the right hand of a 68-year-old hemiplegic female patient with complex regional pain syndrome (shoulder–hand syndrome) (CRPS-SHS) after hemorrhagic stroke: (A) Before combined treatment with biphosphonates and lymphatic drainage type Leduc, mild osteopenia with patchy bone demineralization within finger’s joints; (B) after 6 months of treatment, with significant improvement of localized bone demineralization.
process, where edema was reduced of about 18.5 mm. Finally, proximately to the olecranic process, edema was reduced at about 23.7 mm. Finally, the patients have X-ray films of the right hand demonstrated an increase of mineralization in the fingers’ joints (Figure 1B).

### Discussion

In the present report, we evaluated the effects of biphosphonates and lymphatic drainage type Leduc in CRPS-SHS, reporting in a 68-year-old hemiplegic female affected by hemorrhagic stroke a great improvement of pain and edema of the right hand, with a significative reduction of bone demineralization. Current therapy of CRPS included sympathetic interruption, selective alpha-2 adrenergic agonist agents (clonidine), corticosteroids, ketamine, mannitol, mannitol combined with dexamethasone, calcitonin, and more recently, biphosphonates [17,18]. The role of physical therapy was still debatable.

Several hypotheses on CRPS pathophysiology focused on sympathetic disturbances: reverberating circuits in the spinal cord [19], the ephaptic crosstalk between peripheral sympathetic efferents and nociceptive afferents [20], and the “turbulence” theory [21]. However, none of these theories has ever been proven to explain CRPS comprehensively, and recent studies have cast doubts on the exclusive role of sympathetic nervous system overactivity [3]. Present views suggested that CRPS is based on central sensitization of pain transmission neurons throughout the nervous system effected by N-methyl-D-aspartic acid (NMDA) complex mechanisms and a major immune contribution from activated glial and astrocyte secretion of chemokines and cytokines that maintained and augmented the process. The entire concept of maintained chronic pain is now viewed as a neuronal activity dependent process [22–26]. One hypothesis was an exaggerated localized neurogenic inflammation that can induce peripheral nerve sensitization [27] and abnormal sensory input integration by the cerebral cortex [28,29]. Some authors suggested that an abnormal sympathetic response that caused vasodilatation alternated with episodes of arterial spasm, edema, pain, and hyperhidrosis. In fact, the paretic upper arm frequently appears painful and edematous with altered tactile sensation. There was no evidence that swelling was lymphatic in nature but most likely represented neurogenic edema [26,29].

The sympathetic system is involved early, and

<p>| Table 3: Scoring system for the assessment of clinical severity of complex regional pain syndrome (shoulder-hand syndrome) after hemorrhagic stroke in a patient before and after 6 months of combined treatment with biphosphonates and lymphatic drainage type Leduc [15] |</p>
<table>
<thead>
<tr>
<th>Symptom or sign (score)</th>
<th>Before treatment</th>
<th>After 6 months treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Strongly expressed</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Moderately expressed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Weakly expressed or absent</td>
<td>0.5</td>
</tr>
<tr>
<td>Reduction of finger flexion</td>
<td>Strongly expressed</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Moderately expressed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Weakly expressed or absent</td>
<td>0.5</td>
</tr>
<tr>
<td>Temperature changes</td>
<td>Strongly expressed</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Moderately expressed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Weakly expressed or absent</td>
<td>0.5</td>
</tr>
<tr>
<td>Discoloration (redness, pallor, or cyanosis)</td>
<td>Strongly expressed</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Moderately expressed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Weakly expressed or absent</td>
<td>0.5</td>
</tr>
<tr>
<td>Sensory disturbances (tenderness, hypoesthesia)</td>
<td>Strongly expressed</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Moderately expressed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Weakly expressed or absent</td>
<td>0.5</td>
</tr>
<tr>
<td>Increased sweating (present or absent)</td>
<td>Strongly expressed</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Moderately expressed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Weakly expressed or absent</td>
<td>0.5</td>
</tr>
<tr>
<td>Maximal total score</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Total score before treatment</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>Total score after 6 months treatment</td>
<td>4.5</td>
<td></td>
</tr>
</tbody>
</table>
Biphosphonates in CRPS

when its function has been returned to normal, pain has resolved in some patients. It may also act as a maintaining component of CRPS. The edema of CRPS had several potential mechanisms: 1) increased capillary filtration capacity, a measure of microvascular permeability; 2) increased stimulation of the lymphatics that is under sympathetic control; 3) neurogenic inflammation. However, the edema’s reduction can be induced by lymphatic drainage. In the present study, we used lymphatic drainage type Leduc daily for 5 days/week and subsequently at alternate days for 2 months. The pressotherapy is a technique with compression sleeves that gradually squeezes the swollen arm before manual lymphatic drainage: this procedure contributes to drain subsequently liquid in the lymphatic vessels. It is also important to bind the arm tighter near the hand and less tight near the axilla.

CRPS treatment was primarily based on the alleviation of pain and reduction of edema. Some authors affirmed that the number of patients presenting a spontaneous resolution of CRPS is high [30]. Others were of the opinion that it rarely occurred [31]. Sympathetic block at the limbs could increase the sympathetic denervation characterizing typically the warm phase of CRPS; so, this procedure should be performed only in the cold phase [18]. The only drug that appeared to be effective, when used preventively, was intravenous or epidural administration of clonidine [32,33]. However, other studies failed to produce convincing evidence that clonidine relieved pain in patients with CRPS [18,34]. In randomized controlled trials, intravenous phentolamine, phenylephrine, reserpine, droperidol, and ketanserin were not more effective than a placebo [35,36]. Intravenous lidocaine 3 g/mL in patients with allodynia affected by CRPS to reduce pain, glucocorticoid therapy, analgesics (including opioids), gabapentin (600–2400 mg/day), and spinal cord stimulation had limited therapeutic efficacy [18]. Ketamine, a noncompetitive antagonist of NMDA, by intravenous subanesthetic and anesthetic doses, has been effective in a great number of patients [37–39]. Physiotherapy as transcutaneous electrical nerve stimulation or kinesitherapy, and psychological approach were further therapeutic options [18].

In CRPS, the bone disease is characterized by increased bone resorption: the cortical erosion with subchondral sclerosis and rarefied bone can be induced by the osteoclasts; they are probably activated by local unidentified factors associated with the disease [1–3]. The pathophysiology of this condition remains obscure, but the relief of most symptoms after biphosphonates administration might indicate that osteoclasts are, at least in part, related to increased bone resorption [40]. There was evidence that deep pain afferents released neurogenic calcitonin gene-related peptide and substance P that stimulated osteoclasts and induced bone resorption [41]. In the present report, 6 months after starting therapy with biphosphonates, the patient with CRPS-SHS reported a regression of most signs and symptoms with also a modification of laboratory evaluations and radiographs. Biphosphonates, powerful inhibitors of bone resorption, are regarded as first choice treatment for malignant hypercalcemia and Paget’s disease of bone, and a useful therapeutic tool for osteoporosis. Biphosphonates counteracted the overactivity of osteoclasts, but in addition, they might interfere with the local production of cytokines. In fact, we may divide biphosphonates into two distinct categories: amino biphosphonates (alendronate and pamidronate), which sensitize macrophages to an inflammatory stimulus inducing an acute-phase response with a transient increase of interleukin (IL)-6, tumor necrosis factor-alpha, and IL-1 [42], and nonaminobisphosphonates (clodronate and etidronate) that can be metabolized into macrophages and that may inhibit the inflammatory response of macrophages [43]. However, aminobisphosphonates in humans can induce an acute-phase reaction only after the first intravenous administration, whereas clinical manifestation of acute-phase reaction do not appear in subsequent administrations [44]. Therefore, given the suggested positive correlation between an increase in cytokines and an increase in CRPS symptoms [45,46], the anti-inflammatory activity caused by the inhibition of the release of inflammatory mediators from activated macrophages may suggest the use of nonaminobisphosphonates (e.g., clodronate) in CRPS. In fact, after a number of encouraging open-label studies [17,47,48], some randomized controlled trials were conducted to evaluate the efficacy of bisphosphonate treatment in CRPS [17]. Two of them evaluated pamidronate using fairly satisfactory study designs. The other two were high-quality studies of clodronate [42] and alendronate [49], respectively. In conclusion, the present case demonstrated the potential use of biphosphonates and lymphatic drainage type Leduc in patients with CRPS-SHS. This mode of therapy appeared to be a viable alternative to
counteract the overactivity of osteoclasts and to manage symptoms and signs of the syndrome, but further investigation is required to determine its reproducibility in large case series.

References

20 Nathan PW. On the pathogenesis of causalgia in peripheral nerves. Brain 1947;70:145–70.
33 Reuben SS, Rosenthal EA, Steinberg RB, Faruqi S, Kilaru PA. Surgery of the affected upper extremity of patients with a history of complex regional pain
Biphosphonates in CRPS