

Memantine Treatment of Complex Regional Pain Syndrome

A Preliminary Report of Six Cases

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Objectives: Recent studies have confirmed the contribution of the central nervous system (CNS) to the pathogenesis of Complex Regional Pain Syndrome (CRPS), because animal models of neuropathic pain syndromes demonstrate an over-expression of *N*-methyl-D-aspartate-receptors in the CNS. The aim of this work was to study the influence of a central acting drug—the *N*-methyl-D-aspartate receptor antagonist Memantine—in patients with CRPS of one upper extremity. Here we present the results of 6 patients treated with Memantine for 8 weeks.

Methods: All patients developed CRPS after traumatic injury to one upper extremity. To document changes during the study, levels of pain were measured after clenching the hand using a numeric pain intensity scale ranging from 0 (no pain) to 10 (maximum pain). Motor symptoms were documented for the fingers (fingertips to palm and fingernails to table) and the wrist (flexion/extension). Furthermore, the force was analyzed using a JAMAR-Dynamometer and a Pinchmeter. For assessment of central changes, functional magnetic resonance imaging and magnetoencephalography were used to further document the results of other experiments in 1 patient. Autonomic changes were photographed and pictures were compared before and after treatment with Memantine.

Results: Six months after treatment with Memantine, all patients showed a significant decrease in their levels of pain which

coincided with an improvement in motor symptoms and autonomic changes. The functional magnetic resonance imaging and magnetoencephalography results provided evidence of cortical reorganization [changes in somatotopic maps in the primary somatosensory cortex (S1)]. These changes returned to a cortical pattern comparable to the unaffected side after treatment with Memantine.

Discussion: Based on these first results, the use of Memantine for treatment of CRPS seems promising and supports the hypothesis of a CNS contribution to the pathogenesis and maintenance of neuropathic pain syndromes.

Key Words: CRPS, neuropathic pain, Memantine, NMDA-receptor, cortical reorganization

(*Clin J Pain* 2007;23:237–243)

The term “Complex Regional Pain Syndrome” (CRPS) describes a disorder previously known as “Sudeck’s atrophy, causalgia or reflex sympathetic dystrophy.”¹ CRPS may develop after a traumatic injury or without any obvious triggering event.^{2,3} CRPS type I is distinguished from type II based on the criteria that a nerve lesion is documented in the latter.⁴ Hence, in CRPS type II the nerve lesion leads to symptoms in the corresponding anatomic projection area.⁵ CRPS occurs mainly in the limbs and is characterized by pain, motor symptoms, sweating, edema, and autonomic changes of the skin (eg, hypertrichosis, abnormal sudomotor activity).^{6–8} These symptoms are defined as the classic diagnostic criteria for CRPS that were described in the 2nd ed. of the International Association for the Study of Pain (IASP) regarding the taxonomy of the disease.⁹

Furthermore, a functional impairment of the affected extremity is frequently observed. The diagnosis is not only based on clinical signs and symptoms. Various diagnostic measurements can also be used (Table 1) to verify the disease.¹⁰ CRPS usually progresses into a chronic disorder and chronic courses result in a low response to standard therapy.¹¹ The current treatment consists of noninvasive and invasive methods with limited effectiveness with the overall aim being the reduction of

Received for publication July 12, 2005; revised October 30, 2006; accepted November 20, 2006.

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Supported by the Ministry of Education and Science, Germany—BMBF (Bundesministerium für Bildung und Forschung) and the grant 01EM0110 from the BMBF.

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TABLE 1. Clinical Signs and Symptoms With Diagnostic Tools for CRPS

Clinical signs	Abnormal skin color, temperature change, abnormal sudomotor activity, edema
Pain quality	Burning pain
x-ray (always both hands)	May provide osteopenia and partial decalcification on affected side
Thermography	Different skin temperature
Scintigraphy	May be positive in the first year of disease in CRPS
Electrophysiology	Gives information about nerve involvement in CRPS II

pain and restoration of function of the affected extremity.¹² A combination of physiotherapy and the use of analgesic drugs is the usual standard treatment.^{13–16} For nonresponders, various invasive methods are recommended ranging from sympathetic blockade for sympathetically-induced symptoms to surgical sympathectomy.^{10,13,17}

In animal models used for the study of neuropathic pain syndromes, it has been proven that *N*-methyl-D-aspartate (NMDA)-receptors are up-regulated in the central nervous system (CNS) and that blocking of these receptors reduces pain levels.¹⁸ As CRPS is considered to be a neuropathic pain syndrome, we hypothesized that NMDA-receptors may be up-regulated in this case as well. Therefore, we treated the patients with the NMDA-receptor antagonist Memantine. The use of Memantine in the therapy of CRPS has not yet, to our knowledge, been reported. Previous studies on the treatment of phantom limb pain with Memantine reported normalization of cortical reorganization: displaced or enlarged somatotopic representation of the painful limb was successfully reversed after treatment.^{19,20} There is increasing evidence that cortical reorganization is causally involved in the maintenance of chronic neuropathic pain.^{21,22}

The aim of this study was to demonstrate a CNS contribution in the development and preservation of CRPS. A pharmacologic intervention using the NMDA-receptor antagonist Memantine was hypothesized to antagonize the central processes to improve the patients' condition.

MATERIAL AND METHODS

Patients

This study was conducted at the Department of Hand, Plastic, and Reconstructive Surgery, BG-Trauma Center at the University of Tuebingen, Germany. All patients were diagnosed with CRPS of one upper extremity according to the criteria of the IASP by the same investigator. The diagnosis was then confirmed or, if necessary, rejected by members of the other clinical investigation groups (Department of Anaesthesia and Psychiatry). Because all patients demonstrated a course with the classic signs and symptoms according to the IASP criteria no further diagnostic measures were needed to obtain the diagnosis. Informed consent was obtained

from each patient, and the study was approved by the Ethical Committee of the Medical Faculty of the University of Tuebingen. Physiotherapy was performed daily following a standardized regimen.²³ Patients were treated 3 times a day over a course of 8 weeks. Each work out was about 45 minutes. The treatment included massage, friction, and traction techniques. The patients were actively and passively moved using the affected joints. Furthermore, they were given the opportunity for voluntary physiotherapy with special soft balls to exercise finger movement. Individually developed dynamic splints were used to passively press the affected joints into wider ranges of movement and various proprioceptive measures were applied as well (glass of peas, etc.).

Autonomic changes were documented before Memantine intake by means of photography. After periods of 8 weeks, and 6 months after treatment, the patients were photographed and the changes were documented again.

Pharmacotherapy

Memantine is a low to moderate affinity, noncompetitive NMDA receptor antagonist, acting directly on the phencyclidine recognition site of the NMDA-receptor channel. It has been marketed in Germany since 1982, initially for the treatment of CNS diseases (Parkinson disease, cerebral and peripheral spasticity, Alzheimer disease, etc.). Because some of the patients were previously on analgesic drug therapy these drugs were discontinued to have the same conditions for all patients. Following this, a general treatment regimen with MST (Morphine) was initiated for a period of 2 weeks before Memantine treatment in an equianalgetic dose for all patients. After this dose was reached the 2 weeks of MST intake served as a baseline using a very potent analgesic drug as a control for comparison to the following Memantine treatment. Afterward, Memantine was prescribed orally with 5 mg per day and increasing doses every second day (5 mg steps). A final target dose of 30 mg/d was defined and was applied twice a day (15 mg/morning and 15 mg/evening). After arriving at the dose of 30 mg/d without any serious side effects, further increase of the daily intake was possible. Memantine was given for 8 weeks.

Pain

The patients were instructed to rate their pain on a numeric pain intensity scale (0—no pain, 10—maximum pain) after active clenching of the hand (5 times). Data was recorded before the application of Memantine, and at 8 weeks and 6 months after Memantine treatment.

Motor Symptoms

Motor function was elected as a target parameter to document a possible improvement of symptoms induced by CRPS treatment, because kinematic studies of target reaching and grip force analysis demonstrated pathologic sensorimotor integration in the parietal cortex in affected patients.²⁴ Consequently, finger and wrist movement may be impaired in many cases. The finger and wrist joints are

known to be excellent parameters for assessment of hand function, and were, therefore, defined as the joints of interest for measuring flexion and extension.²⁵ Motor symptoms were documented before Memantine treatment, and after 8 weeks and 6 months after that. Finger movements were assessed using 2 different tests as follows: the patients were asked to make a fist. Incomplete fists were documented taking note of the distance between the fingertip of the impaired finger and the palm in centimeters. The same was done with the extension of the fingers while the patient had the back of his hand lying on the table. Impaired finger extension was noted with the distance between the fingernail and the underlying surface of the table in centimeters as well.²⁶

If more than one finger was impaired, the deficits of the affected fingers (for flexion or extension) were summed up to one value. Furthermore, the active range of wrist motion was measured with a goniometer for extension and flexion, whereas force was estimated by means of a computerized dynamometer. The patients had to push a JAMAR-dynamometer with their hand until the maximum strength was reached at level 2 of the dynamometer scale. To evaluate the strength of the pinch maneuver a computer-linked pad (3 × 3 cm) was placed between the thumb and index finger. The data for both tests were recorded using Biometrics software (Penny and Gilles, Munich/Germany). All data regarding force were expressed in kilograms and compared with that obtained for the unaffected side as usually formulated for data evaluation.^{27,28}

Magnetoencephalography and fMRI

Magnetoencephalography (MEG) was used to study changes in the cortical organization of the primary somatosensory cortex (S1). For assessment of cortical activity, somatosensory evoked fields were recorded using a whole head magnetoencephalographic (MEG) system (CTF, Inc, Vancouver, Canada) with 151 first-order gradiometers. Sensory evoked fields were obtained by pneumatic stimulation (trials: 400, stimulus duration: 100 ms; interstimulus interval: 500 ms ± 50 ms, sampling rate: 612.5 Hz) of the thumb and little finger on the affected and the unaffected side, before and after treatment. The functional organization of S1 was determined by dipole analysis of the first prominent peak of the magnetic brain response. The localization was represented in a 3 dimensional grid and was expressed as the angle "θ" between Cz and a direct line from the middle of the sphere to the dipole localization.²⁹ Cortical reorganization was expressed as the difference between the θ angle of the cortical distance DI/DV of the affected side mirrored in the unaffected side in S1.

Due to the technical effort required only 1 patient underwent MRI scanning in a supine position at 3T (Siemens Trio, 8 HF-head-coil) with 30 oblique transversal slices (3 mm thickness, 1 mm gap) covering the whole head using a T2*-weighted echo-planar imaging sequence (TR = 2.5 s, matrix size = 64*64, TE = 30 ms, flip angle = 90 degrees). The patient was in supine position on

the padded scanner couch and wearing hearing protection while scanned. Additionally, a T1 weighted 3D image (MPRage; TR 2.3 s; TE: 3.93 ms; 160 sagittal slices 1 + 0.5 mm) was acquired.

Spatial preprocessing and data analysis were performed using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/spm2.html>). Each time-series was realigned and resliced after unwarping in phase encoding direction (anterior/posterior) to account for susceptibility in mesolimbic areas and movement artifacts. Images were normalized to the MNI-reference to provide normalized location of activation maxima and to compare the premeasurement and postmeasurement within the same voxel space. To correct for intensity inhomogeneities echo-planar images were smoothed with a Gaussian filter of 9 mm (FWHM).

A design matrix for executed movements after minus before treatment was calculated using a high-pass filter of 128 seconds. Significant activation sites are given for areas of $P < 0.001$, after correction for false-positive responses within the whole brain volume (FWE).

The patient was tested before and 8 weeks after treatment with Memantine. Blood oxygenation level dependent response was recorded during fist clenching movements, in a block design (6 blocks, rest), first with the affected limb, and then with the unaffected limb. To control for equal hand-grip strength, the patients pressed a rubber ball of a vigorimeter.

Statistical Analysis

Data regarding levels of pain and motor symptoms were analyzed with analysis of variances (ANOVAs). For expected values, 95% confidence intervals (CIs) were computed.

The pain values of the 6 patients were assessed 3 times on a pain intensity scale (before Memantine treatment, and 8 wk and 6 mo after treatment with Memantine). These data were analyzed by the factors *time* and *Memantine treatment* (8 wk/6 mo).

To analyze the effect of treatment on finger movement, data recorded for the fingertips to palm task (after clenching a fist and moving the fingernails to the table while extending the fingers) were used in 2 ANOVAs with the same factors as mentioned above. With a similar set of ANOVAs, we estimated the effect of Memantine treatment on the range of wrist movement (one for extension, and the other for flexion). One patient was excluded from the analysis of wrist movement, because he underwent an operative arthrodesis of the wrist (Table 2).

Finally, 2 ANOVAs were performed to analyze the data on the augmentation of force as measured using the dynamometer and pinch-meter. Data collected from the functional magnetic resonance imaging (fMRI) and MEG measurements are expressed as means and standard deviations. All ANOVAs were calculated based on the 2 factors *patient* and *time*.

RESULTS

Four men and 2 women (age range 29 to 64 y; mean age 48.3 y) with CRPS were included in this study

TABLE 2. Patient Sample

Patient	1	2	3	4	5	6
Sex	M	M	M	F	M	F
Age	59	50	29	31	64	58
Patient history	Wrist distortion	Fracture of the wrist	Cut injury of flexor tendons and median nerve	Wrist distortion	Elective surgical intervention (arthrodesis of the wrist)	Simple cut injury
CRPS type I/II	I	I	II	I	I	I
Pain duration (mo)	7	23	4	13	18	9
Affected side	L	R	R	R	L	L
Pharmacologic therapy			NSAIDs	NSAIDs, oral opioid		NSAIDs
Physiotherapy and duration	Yes, 6 mo	Yes, 19 mo	Yes, 4 mo	Yes, 10 mo	Yes, 13 mo	Yes, 7 mo
Occupation	Farmer	Factory worker	Farmer	Baker	Construction worker	Pensioner
Comorbidity	Diabetes mellitus (type II)	None	None	None	None	None

NSAID indicates nonsteroidal anti-inflammatory drugs.

between December 2002 and July 2004. Patients' characteristics are shown in Table 2. All patients underwent physiotherapy before their first visit in our clinic. The total time of physiotherapy performed is depicted in Table 2. Patient No. 3 was the only case with CRPS type II, whereas all the other patients had type I. Due to the small number of patients, the prevalence of CRPS type II in this sample population, with regard to the ratio of type I versus type II, did not represent the data described in normal populations.² Six months after treatment with Memantine 5 of the 6 patients were able to return to their jobs without impairment, although under some circumstances, demonstrating only minor disabilities. Patient 4 had to leave her old profession in a bakery and successfully started a new job in an office. Patient 2 stopped the Memantine-intake after the study, whereas the other patients continue to take Memantine on their own request in the same fashion as they received it during the study.

Pain Levels

No continuous pain was evident in any of the participating patients 6 months after treatment. To analyze the influence of Memantine on pain after clenching of the affected hand (5 times) 6 patients were examined at the three assessment dates using a numeric pain intensity scale (0 to 10). The effect of time after Memantine treatment at the assessment dates had a *P* value of less than 0.0001 (*F*-ratio: 286.95). The least square means of the levels of pain were 9.17 immediately before treatment with a 95% CI ranging from 8.55 to 9.78. After 8 weeks of Memantine application pain levels decreased on the numeric pain intensity scale to a score of 1.00 (95% CI: 0.39-1.61). Six months after treatment with Memantine the average level was 1.17 (95% CI: 0.55-1.78) (Fig. 1).

Motor Symptoms

Range of finger motion was clearly different over the course of the 3 different assessments. The *P* value for the fingertips to palm task was smaller than 0.0001 (*F*-ratio: 78.42) and 0.0014 (*F*-ratio: 34.41) for the fingernails to table task. Accumulated distances of fingertips to palm started with 17.5 cm (95% CI: 15.6-19.4 cm, *P* value < 0.0001)

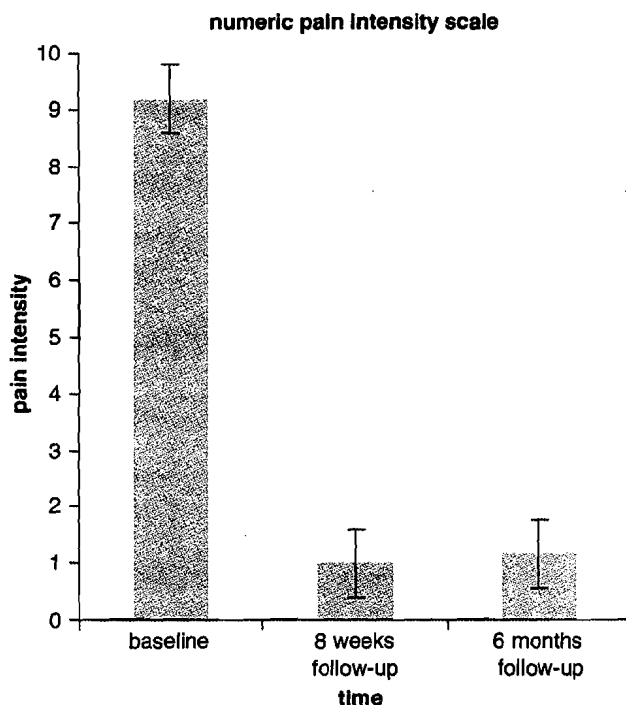


FIGURE 1. Pain intensity (numeric pain intensity scale) before treatment, 8 weeks, and 6 months follow-up after Memantine treatment. Pain levels after clenching the affected hand several times (least squared means and 95% CIs, *n* = 18).

on the first measurement and was reduced to 5.5 cm (95% CI: 3.6-7.4 cm) after 8 weeks of treatment with Memantine. The distance was finally 3.3 cm (95% CI: 1.4-5.3 cm) after 6 months of treatment. The sum of the distances from the fingernails to table task was 7.5 cm (95% CI: 6.3-8.7 cm) before treatment with Memantine. After 8 weeks of Memantine-intake this distance was reduced to 3 cm (95% CI: 1.8-4.2 cm). After 6 months an average distance of 1.5 cm could be reached during this task (95% CI: 0.3-2.7 cm) indicating a significant improvement in the range of finger movement (Fig. 2).

In wrist movement, the mean range of *extension* started at -23 degrees (95% CI: -18 to -28 degrees, *P* value 0.0006, *F*-ratio: 21.71) at the first examination of the patients before Memantine application. After 8 weeks of treatment it was increased to -35 degrees (95% CI: -30 to -40 degrees) until the maximum of -43 degrees was reached after 6 months of Memantine treatment (95% CI: -38 to -48). The mean for wrist range of *flexion* was 28 degrees (95% CI: 22-34 degrees) at the first session, and improved to 41 degrees (95% CI: 35-47 degrees) after 8 weeks with Memantine. After 6 months, *flexion* of the wrist was increased to 54 degrees (95% CI: 48-60 degrees).

Additionally, the development of force, as measured using the JAMAR-dynamometer and pinchmeter, also demonstrated a significant improvement over time. Dynamometer force on the first presentation was 13.8% of the unaffected hand (95% CI: 7.1%-20.6%; *P* = 0.0185; *F*-ratio: 18.90), and improved to 27.3% (95% CI: 20.6-34.1 N) after 8 weeks. Six months after beginning the Memantine treatment the force calculated with the dynamometer increased to 40.2% (95% CI: 33.4%-47%) of the unaffected hand. The corresponding pinchmeter values were 20.3% (95% CI: 16.1%-24.5%; *P* = 0.0071, *F*-ratio: 36.96) before Memantine treatment, 29.5% (95%

CI: 25.3%-33.7%) after 8 weeks, and 43.2% (95% CI: 39%-47.4%) 6 months after treatment. With clinical improvement of force and range of motion, a decrease in the corresponding autonomic changes was also observed to various degrees in all patients.

MEG

Before treatment patient No. 1 demonstrated an asymmetry in the θ angle of the dipoles calculated from the somato-sensory evoked responses to stimulation of the thumb versus little finger. This difference was seen in the S1 cortex of the affected limb unlike the contralateral unaffected limb (difference θ angle -11 degrees). After therapy, the somatosensory evoked responses to stimulation of the thumb versus little finger were increased in the cortical areas representing the affected limb and were comparable to those of the unaffected side.

fMRI

Treatment-induced changes resulted in blood oxygenation level dependent response decrease bilaterally in the primary somatosensory cortex (S1 left, *t* = 8.23; S1 right, *t* = 6.66) during fist clenching movements of the affected limb in patient No. 1 (Fig. 3).

Drug Induced Side Effects

During the whole observation period no serious side effects were observed. One patient who was known to have Diabetes Mellitus observed slightly decreased blood sugar level values. Another patient reported

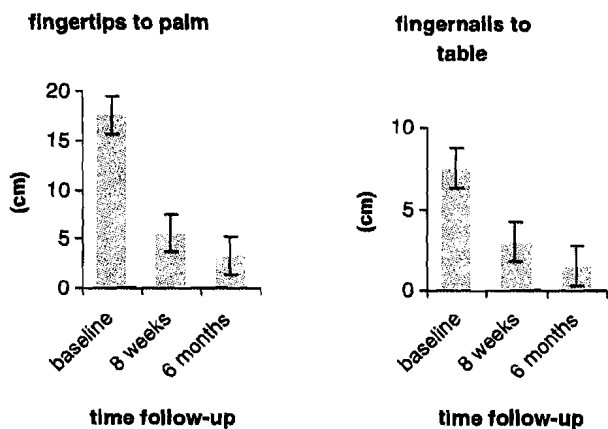


FIGURE 2. Distance in centimeters between fingertips and palms during active finger flexion and the distance in centimeters of the patients' fingernails on the surface of a table while the hand was on its dorsal side attempting to extend fully the finger joints (least squared means and 95% CIs, n=18).



FIGURE 3. Differences in blood oxygenation level dependent between pretreatment and posttreatment measurements during fist clenching with the affected limb in one typical patient (No. 1). Higher activations of S1 bilateral during baseline.

cognitive problems with difficulties in concentration after increasing the daily Memantine-dose from 30 to 40 mg. The symptoms disappeared after the dose was reduced to 30 mg.

DISCUSSION

The present data support the hypothesis of CNS involvement in the pathogenesis and maintenance of CRPS type I. Normalization of cortical reorganization after treatment with Memantine, as evidenced by fMRI and MEG was observed in the one exemplary patient after treatment with Memantine. The involved cortical areas clearly demonstrated abnormal activity before Memantine treatment. After 8 weeks of treatment these abnormalities were shown to decrease to a value comparable to the corresponding cortical sites of the unaffected limb.

Recently, it has been shown that there is an increased density of NMDA-receptors in the CNS of animals with neuropathic pain syndromes.³⁰ At present, the mechanism leading to the overexpression of these receptors remains unclear, and whether it plays a role in the pathogenesis of CRPS remains to be determined.³¹ NMDA-receptor up-regulation may occur secondary to CRPS-related changes in cortical function. As a non-competitive antagonist of NMDA-receptor activation under physiologic conditions, Memantine is hypothesized to leave the receptor with a mild depolarization, still allowing its physiologic activation.³² With pathologic activation of the NMDA-receptors-as in CRPS-Memantine is capable of a tonic blockade of these receptors.³³ Under these circumstances, Memantine is supposed to have a "neuroprotective" effect.³⁴ A possible NMDA-receptor up-regulation in CRPS may not be a specific issue of this disease, nevertheless may be of importance in other neuropathic pain syndromes, for example, in phantom limb pain.

Patient No. 1 demonstrated, as evidenced through fMRI and MEG, cortical reorganization in areas representing the affected limb in comparison to the unaffected limb before Memantine treatment. With cortical normalization, a clinical improvement of the observed signs and symptoms was also found in this patient (see Results). There was a clear decrease in the level of pain measured with the numeric pain intensity scale from the time before therapy to 8 weeks, and 6 months, after Memantine treatment. Although only a few cases are presented in this report, the reduction in the levels of pain is significant. Moreover, the functional results demonstrate an impressive improvement in the range of motion after Memantine-treatment with increasing values for wrist and finger movement. Even the strength increased 6 months after Memantine application as estimated by the JAMAR-dynamometer and the pinchmeter. The results obtained for the motor symptoms document the clinical benefit. These excellent functional results and the reduction of pain lead to the successful return of all patients but one to their old profession.

Furthermore, all of these patients demonstrated a prominent amelioration of the autonomic symptoms.

Reviewing these initial results of six patients suffering from CRPS, one is tempted to speculate that the treatment of CRPS with Memantine may constitute a highly efficient treatment leading to normal hand function and decreased levels of pain. However, no control group undergoing physiotherapy and "activity of daily life" alone without pharmacologic intervention was used. The exercises with various dynamic splints to improve active and passive range of movement may itself play a significant role in improvement. Therefore, Memantine alone may not be responsible for these results. However, this is extremely unlikely because in the more than 100 patients that are treated with CRPS of the hand per year in our clinic none of them showed comparable recovery with physiotherapy and standardized treatment alone. Though it still remains difficult to conclude a clinical benefit based on a therapy with Memantine because all patients received this kind of pharmacologic treatment.

Another problem seems to be the small number of cases, which does not provide the possibility for further statistical analyses. Furthermore, only one patient in our study presented with CRPS type II, which represents a fraction of 17% of the examined individuals. In normal clinical practice we observe a ratio between 30% and 60% of CRPS type II cases, originating from various nerve injuries, respectively (cut injuries, compression syndromes, etc.).

In general, it seems that patients treated with Memantine participated with higher motivation in their daily physiotherapy sessions without restrictions due to pain. Thus, they performed their exercises consistently. Nevertheless, other strategies have been proposed in the past to break through the circle of pain before long lasting stiffness and atrophy develops in the affected limb.^{35,36} Invasive measures such as sympathetic blockade of the upper limb are still a common treatment option in nonresponding cases.³⁷ Leaving the upper limb without proprioception due to this measure, however, may lead to an unintended side effect of partial or even complete paralysis which disturbs physiotherapeutic treatment.³⁸ Therefore, it should be an overall aim to avoid invasive measures in treating patients in this condition.

To conclude, our preliminary results gathered on 6 patients with CRPS of one upper extremity treated with Memantine support the hypothesis that cortical reorganization is involved in the disease process. Furthermore, the data demonstrate a substantial clinical improvement with the use of pharmacologic measures that antagonize these cortical changes in the CNS. However, the lack of a suitable control group precludes the drawing of firm conclusions.

ACKNOWLEDGMENTS

The authors are grateful for the excellent support of B. Wasserka (Institut für Medizinische Psychologie und Verhaltensneurobiologie, Eberhard-Karls Universität

Tübingen) and M. Trick (Klinik für Anästhesiologie und Transfusionsmedizin, Abteilung für Anästhesiologie und Intensivmedizin, Eberhard-Karls Universität Tübingen). The authors also thank W. Grodd and M. Erb for technical support (fMRI) and R. Vonthein (Institute for Medical Biometry at the University of Tübingen) for his statistical consultation.

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Trauma

Early Diagnosis in Post-traumatic Complex Regional Pain Syndrome

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 ORTHOPEDICS 2007; 30:450

June 2007

Complex regional pain syndrome is characterized by the presence of regional pain and sensory changes following a predominantly traumatic noxious event.

Complex regional pain syndrome is a severe complication in orthopedic surgery. Trauma patients undergoing orthopedic procedures frequently develop complex regional pain syndrome, particularly the hand or forearm. It is characterized by the presence of regional pain and sensory changes following a predominantly traumatic noxious event. Pain is associated with abnormal skin color, skin temperature, abnormal sudomotor activity, and edema. Two types of complex regional pain syndrome can be distinguished: the former termed "reflex sympathetic dystrophy," occurs without a definable nerve lesion, whereas the latter termed "causalgia," refers to cases where a definable nerve lesion is present.¹

The diagnosis of complex regional pain syndrome is predominantly based on clinical signs and symptoms. Various laboratory tests or imaging procedures have been applied in complex regional pain syndrome. However, most of these tests have not been evaluated with regard to their sensitivity (ie, the probability that a patient with complex regional pain syndrome will have a positive test result) and specificity (ie, the probability that a patient without complex regional pain syndrome will have a negative test result). No consensus exists on the criteria for diagnosing complex regional pain syndrome or reflex sympathetic dystrophy and even with the new definitions of complex regional pain syndrome, interobserver reliability and specificity is still poor and depends on the criteria used.

Another important limitation is a consequence of the progressive nature of complex regional pain syndrome. In early stages, edema and increased skin temperature may be observed, whereas in later stages signs of dysregulation decrease but pain may persist. Diagnostic tests useful in early stages of the disease may fail. Furthermore, signs and symptoms may change quickly. As a result, in many studies correlations between clinical findings, stage of the disease, and laboratory tests are not reported. Combined, these limitations impede the determination of the diagnostic value of different test procedures used in complex regional pain syndrome.

Nevertheless, it is important to establish an early diagnosis if it appears after trauma or surgery. This article provides an overview of the clinical implications of tests and procedures in diagnosing complex regional pain syndrome.

Clinical Signs and Symptoms

Since complex regional pain syndrome is a clinical diagnosis, the appearance of a typical constellation of signs and symptoms is fundamental for establishing the diagnosis. In 1995 the definition of complex regional pain syndrome was established by a Consensus Committee. A few years later, advanced diagnostic criteria were published for the clinical diagnosis.^{1,2} The criteria of clinical symptoms are shown in Tables 1 and 2.

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Table 1
Clinical Complex Regional Pain Syndromes*
Spontaneous pain or allodynia/hyperalgesia that is not limited to the territory of a single peripheral nerve and is disproportionate to the inciting event.
Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain.
This diagnosis is precluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.
*Stanton-Hicks et al. ¹

Table 2
Advanced Diagnostic Complex Regional Pain Syndrome Criteria ²
Continuing pain that is disproportionate to the inciting event.
Must report at least one symptom in each of the following four categories:
Sensory: reports of hyperesthesia.
Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry.
Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry.
Motor/tropic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or tropic changes (hair, nail, skin)
Must display at least one sign in two or more of the following categories:
Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch).
Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry.
Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry.
Motor/tropic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or tropic changes (hair, nail, skin).
*Bruehl et al. ²

Tests to Verify Clinical Findings

Inter-rater reliability is poor in the clinical diagnosis of complex regional pain syndrome and clinical difficult to evaluate; laboratory tests are helpful to verify the diagnosis. A hand volumeter can be used to evaluate edema by measuring the fluid overflow displaced by water comparing the healthy and diseased limb.

With motor disturbances, a goniometer is necessary to assess active or passive range of motion or dynamometer and hand function questionnaires (eg, disability of arm, shoulder, hand or the Michigan questionnaire) can register the degree of disability due to reduced hand function.^{6,7} Measurements can be performed using a visual analog scale.⁸

The assessment of temperature side differences in complex regional pain syndrome is mandatory for establishing the diagnosis and can be done with an infrared thermometer at different measuring points or by using thermal imaging. However, the dynamic character of this phenomenon (depending on disease duration and environmental factors) must be taken into account.

While in healthy patients only slight differences in skin temperature between sides have been documented (hands, $0.24 \pm 0.23^\circ\text{C}$; fingers, $0.15 \pm 0.15^\circ\text{C}$), in patients after hand or wrist trauma without any complication, temperature differences of $0.9^\circ\text{C} \pm 0.8^\circ\text{C}$ were reported up to 8 weeks after trauma.^{9,10} In patients with complex regional pain syndrome, side-to-side temperature differences of 0.6°C , 0.8°C , or 1°C have been observed indicating high statistical significance. However, there is a substantial overlap with trauma patients lacking complex regional pain syndrome: a useful diagnostic threshold should be set at a side-to-side difference of 1.5°C to differentiate between normal physiological post-traumatic changes and complex regional pain syndrome.



Figure 1: Clinical findings of post-traumatic complex regional pain syndrome I of the left hand.

complex regional pain syndrome I.¹¹⁻¹³

Other clinical findings include sensory impairment that can be “positive” (ie, allodynia, mechanical, and thermal hyperalgesia) or “negative” (ie, hypesthesia, hypalgesia). Sensory findings are observed in a localized (ie, glove-like) and generalized (ie, u hemisensory) distribution.¹⁴ Quantitative sensory testing to confirm findings of sensory abnormalities was applied; however, the results are not specific for complex regional pain syndrome and do not provide additional diagnostic information. This method is not recommended as a routine laboratory test for the diagnosis of complex regional

Sympathetic Function Tests

Numerous studies revealed evidence for malfunction of the autonomic nervous system in patients with complex regional pain syndrome. The interpretation of these findings is controversial, but the existence of autonomic disturbances, particularly in the early phase of complex regional pain syndrome, is unquestionable. This phenomenon can be assessed in various ways, leading to different diagnostic procedures with various approaches.

The peripheral vasoconstrictor reflex, mediated by β -adrenergic sympathetic fibers, can be assessed by Doppler flowmetry or thermography using different stimuli (whole body warming, arousal maneuver, or sweating). Qualitative methods exist that visualize the sweat response, or indirect methods like the Tinel sign. Sympathetic skin response potentials (sympathetic skin response) can be applied.¹⁵ Alternatively, sweat output can be quantified by gravimetric measurement. Local sweating can be induced through an axon reflex (quantitative sudomotor axon reflex test). The resting sweat output as well as the sweating induced by raised body temperature (thermoregulatory sweating, thermoregulatory sweat testing, central stimulation) can be recorded.¹⁶

While vasoconstrictor activity is lowered in complex regional pain syndrome, sudomotor function is either decreased (resting sweat output) or enhanced (thermoregulatory sweat testing, quantitative sudomotor axon reflex test). Laboratory tests described are a useful diagnostic tool for complex regional pain syndrome; however, they are difficult to conduct and none could reach clinical importance due to the lack of standardization and

Neurophysiological Tests

The diagnosis of complex regional pain syndrome type I excludes—by definition—the presence of peripheral nerve lesion and therefore nerve conduction velocity abnormalities are not expected. However, the diagnosis of complex regional pain syndrome type II requires a peripheral nerve lesion and complex regional pain syndrome II following central nervous lesions, eg, brain infarction or brain tumors. Since signs and symptoms of complex regional pain syndrome I and II may be very similar, neurophysiological testing is important in differential diagnosis of complex regional pain syndrome to confirm or to exclude major peripheral nerve or central nervous system pathology.

With respect to nerve conduction velocity testing, discrete abnormalities on nerve conduction velocity are observed due to edema or peripheral vasoconstriction.^{15,20} Distinct abnormalities >20% of normal are noted and may indicate underlying peripheral nerve lesion, eg, carpal tunnel syndrome or complex regional pain syndrome II. Electromyography recordings were not routinely applied in clinical studies in complex regional pain syndrome patients because electromyography is painful and may worsen complex regional pain syndrome.

With respect to somatosensory-evoked potentials after median/ulnar or tibial nerve stimulation in complex regional pain syndrome I patients, somatosensory-evoked potentials reveal normal results in the majority of patients. In a few patients, borderline delay of latencies or amplitudes. In patients with suspected complex regional pain syndrome II (severe trauma, localized sensory, or motor abnormalities consistent with peripheral nerve or root lesion), somatosensory-evoked potentials may be pathological. Particularly in complex regional pain syndrome II, somatosensory-evoked potentials may be helpful, as proximal nerve or central nervous system lesions cannot be detected by nerve conduction velocity measurements.

In complex regional pain syndrome patients with signs of central nervous system dysfunction, eg, depression, anxiety, or dystonia, somatosensory-evoked potentials recordings may be useful. Normal results in complex regional pain syndrome patients may be due to functional neuroplastic changes and further diagnostic procedures (ie, magnetic resonance imaging [MRI] of the brain or spinal cord, lumbar puncture) are only required if the clinical

structural central nervous system lesions.¹⁴

Neurophysiological tests are useful in the differential diagnosis of complex regional pain syndrome as a peripheral nerve or central nervous system lesion; however, the findings are not specific for the condition.

Assessment of Inflammatory Parameters

As first described by Sudeck,²⁷ clinical symptoms of complex regional pain syndrome reveal similar to a systemic inflammatory reaction. Within the past few years, several studies on arterial blood flow, oxygen utilization, and skin temperature in complex regional pain syndrome as well as spectroscopic and scintigraphic studies were conducted. These studies supported the hypothesis that an exaggerated inflammatory response may play an important role in the pathogenesis of complex regional pain syndrome. However, the laboratory abnormalities observed in these studies were not specific for complex regional pain syndrome. Thus the tests applied were predominantly of scientific interest.

For clinical purposes, it is important to distinguish complex regional pain syndrome from a local infection (e.g., osteomyelitis, erysipelas) that may have similar clinical findings. Laboratory tests in complex regional pain syndrome show parameters that mediate a systemic inflammatory response (C-reactive protein, erythrocyte sedimentation rate, leukocyte count) are not elevated in complex regional pain syndrome whereas neuroinflammatory markers (substance P, bradykinin, and calcitonin gene-related peptide) were increased compared to healthy controls. This finding also supports the assumption of a localized inflammatory response that might be triggered by a peripheral nerve injury mechanism. For differential diagnosis, this important finding points out that in patients with symptoms of complex regional pain syndrome but increased findings of generalized inflammation (erythrocyte sedimentation rate, C-reactive protein, and leukocytes increased), other causes of inflammation should be excluded (Table 3).

Table 3 Differential Diagnoses of Complex Regional Pain Syndrome
Soft-tissue infection
Osteitis
Fracture nonunion
Rheumatoid arthritis
Neurological disorders (ie, polyneuropathy, neuritis, etc)
Malignant tumors

Psychological Assessment

With respect to psychopathology, no compelling evidence exists that complex regional pain syndrome is a psychogenic condition or that certain personality traits predispose one to develop complex regional pain syndrome.^{24,25} In different studies, an increased frequency of anxiety and mood disorders has been observed in complex regional pain syndrome patients. However, compared to patients with other chronic pain disorders (headache, back pain, neuropathic pain), the prevalence of psychological distress is higher in complex regional pain syndrome patients. This evidence exists that complex regional pain syndrome patients display more psychological distress than other chronic pain patients.

Therefore, psychological abnormalities are not pathognomonic but may precede, accompany, or be a consequence of complex regional pain syndrome. Recommendations for the use of psychological questionnaires should follow the general guidelines of the Psychiatric and Psychological Societies and should be adapted to the clinical situation.

Imaging Methods

Radiography

Since Sudeck²⁷ described the typical radiographic changes on plain radiographs of the affected extremities, conventional bilateral radiographs of the hand are standard for diagnosing complex regional pain syndrome. The primary radiographic manifestations are diffuse osteoporosis with a severe patchy demineralization, soft tissue swelling, and joint space narrowing.

especially of the periarticular regions, combined with a subperiosteal bone resorption (Figure 2). In the middle of the past century, several authors noted evidence of a radiographic progression paralleled to the clinical disease activity.^{28,29} Later, typical radiological findings in complex regional pain syndrome patients were supposed to be unspecific and to appear late during the course of the disease. Prospective studies about particular findings and their clinical relevance are rare.

Bickerstaff et al,³⁰ who investigated radiographic changes in patients after Colles' fracture with and without complex regional pain syndrome interpreted the similarity of disuse demineralization and complex regional pain syndrome, related demineralization as an effect of a common pathogenesis. They found a more marked and prolonged bone loss in complex regional pain syndrome patients compared to immobilized trauma patients. This bone loss occurs more markedly at trabecular bone but increased endosteal resorption of cortical bone is also a feature. The extreme loss of function in complex regional pain syndrome | accelerate the bone demineralization process.



Figure 2: Radiological findings of complex regional pain syndrome of the hand.

By applying a semi-quantitative scoring system for classifying the demineralization findings in 274 Colles' fracture a positive predictive value of 83% was reported 7 weeks after trauma (sensitivity 81%, specificity 75%). The scoring system consisted of a combination of features that are apparent at sites of trabecular bone loss. These comprise a generalized loss of density, patchy radiotranslucencies, subchondral radiotranslucencies, and loss of trabecular definition.³¹ Our findings could not confirm these results in a study with similar design. In a study with similar design, radiological examiners who were blinded towards the clinical findings of the patients. This investigation showed a high specificity of radiological findings 8 weeks after trauma, but a fair sensitivity of 36%, leading to a positive predictive value of 58% in 175 patients after distal radial fracture. This data showed a high number of patients with clinical symptoms of complex regional pain syndrome that did not expose the typical radiological findings. The underlined assumption is that radiographic changes appear late during the course of the disease and therefore radiography does not qualify as a screening procedure.³²

Three-phase Bone Scan



Figure 3: Three-phase bone scan in complex regional pain syndrome of the left hand.

Three-phase bone scans have been used for three decades to diagnose complex regional pain syndrome. In particular, Kozin et al established the characteristic pattern of scintigraphic findings present in complex regional pain syndrome patients. An increased blood flow into the affected limb combined with an increased uptake during the blood pool phase and an increased periarticular uptake during the delayed static phase are supposed to be pathognomonic for complex regional pain syndrome (Figure 3).³⁵ According to changes in the picture during the course of the disease, the scintigraphic findings are subjected to changes that should provide useful information about the therapeutic effects.³⁶

Most of the published studies present data about retrospective patient populations that underwent three-phase bone scan examination.^{37,38} Diffusely increased juxta-articular tracer uptake in the delayed images was found to be the most sensitive indicator for complex regional pain syndrome. In these studies only patients with a clinical suspicion for complex regional pain syndrome were examined.

The results are limited due to bias in patient selection. The prevalence of complex regional pain syndrome in the aforementioned study populations did not reflect the actual incidence of the disease in an unselected patient population.³⁹

Prospective studies describing the diagnostic power of three-phase bone scan in complex regional pain syndrome are rare. Todorovic et al⁴⁰ investigated complex regional pain syndrome patients after trauma using a three-phase bone scan and radiography and found a high sensitivity with a positive predictive value of 97% in the bone scan and a positive predictive value of 73% in the radiography, whereas the radiography reached a sensitivity of 73% and a positive predictive value of 97%. These results must be carefully interpreted because only patients with clinical suspicion for complex regional pain syndrome were examined (n=20). The control group consisted of one patient.

Bickerstaff et al³² compared 16 patients with post-fracture complex regional pain syndrome to 6 pa-

fracture healing and found significantly elevated periarticular uptake in the complex regional pain syndrome. In our recent study 175 patients after distal radial fracture were prospectively followed for 4 months; bone scan was performed twice. Two blinded observers detected signs for complex regional pain syndrome in 16% of the clinically diagnosed complex regional pain syndrome patients 8 weeks after trauma. In terms of sensitivity, a high specificity was found in the same study.

A meta-analysis of 19 articles relating three-phase bone scan to complex regional pain syndrome in the extremity also revealed a poor sensitivity of approximately 50% of this diagnostic method. The three-phase bone scan decreases with the duration of the disease.^{39,41} This observation suggests that in the disease the characteristic changes in soft tissue and bone that lead to the pathological scintigraphy normalize and are replaced by a centralization of the symptoms.

Three-phase bone scan appears to be a good diagnostic tool in non-trauma patients. For the early normal post-traumatic states and complex regional pain syndromes, this diagnostic method does not have high accuracy.

Magnetic Resonance Imaging

Since MRI allows visualization of soft-tissue and bone structure with high resolution, it has become useful in diagnosing various musculoskeletal disorders. Several authors suggested its application for diagnosing complex regional pain syndrome I.

Magnetic resonance imaging examination in complex regional pain syndrome I patients revealed changes that change during the course of the disease in a characteristic manner.⁴² Skin thickening and bone changes in carpal and metacarpal bones as well as effusions of adjacent joints are supposed to be characteristic of the acute and early phase of complex regional pain syndrome I.^{43,44}

Magnetic resonance imaging is commonly performed with T1- and T2-weighted sequences and T1-weighted sequences with fat suppression before and after intravenous administration of contrast material (gadolinium). Koch et al⁴⁵ questioned the diagnostic value of MRI in diagnosing complex regional pain syndrome I among 17 clinically diagnosed complex regional pain syndrome I patients only 1 patient with typical MRI findings. Our data obtained in MRI investigation in 175 patients 8 and 16 weeks after distal radial fracture revealed a sensitivity of MRI that decreased from the 8th week to the 16th week investigation (43% to 14%) and a specificity of 78% in the 8th week to 98% in the 16th week investigation. These results suggest that the consequences of trauma or surgery mimic complex regional pain syndrome I-like MRI findings. In complex regional pain syndrome disease patients often present without typical MRI findings. Thus MRI is not a useful screening method, but may be helpful in the exclusion of differential diagnoses.

Summary

Since prospective studies confirmed an incidence of >10% of complex regional pain syndrome I in patients after distal radial fracture, early diagnosis is important.^{32,46} Therapy should be commenced as early as possible using a systematic approach to avoid chronicity of the disease. Despite this, epidemiological studies reveal a delay in effective treatment among complex regional pain syndrome patients, who were repeatedly referred to different physicians and often treated inadequately before being referred to specialized pain clinics.

In post-traumatic patients, the clinical examination still is preferred to establish the diagnosis of complex regional pain syndrome. First, possible differential diagnoses must be excluded. Next the clinical criteria of the definition should be checked and documented, if possible with the help of verifying procedures. Imaging could be applied; however, they are not useful for early diagnosis since sensitivity is low and the consequences of trauma may interfere with potential complex regional pain syndrome findings. In questionable cases, repeat examinations after short periods detect the presence of complex regional pain syndrome in orthopedic patients particularly if symptoms are progressive or an expected improvement does not occur.

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