STUDY

Intervention for Erythromelalgia, a Chronic Pain Syndrome

Comprehensive Pain Rehabilitation Center, Mayo Clinic

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Objective: To describe the response in patients with erythromelalgia to the pain rehabilitation program at Mayo Clinic, Rochester, Minnesota.

Design: Retrospective case series.

Setting: Comprehensive Pain Rehabilitation Center at a tertiary referral medical center.

Patients: Eight patients with erythromelalgia admitted to the pain rehabilitation program from January 1, 2002, through June 30, 2007.

Main Outcome Measures: The Multidimensional Pain Inventory, the 36-Item Short Form Health Survey, the Pain Catastrophizing Scale, and the Center for Epidemiologic Studies Depression Scale were administered at admission and dismissal from the program. Mean differences in scores were compared using 2-sided paired *t* tests.

Results: Scores for the life interference, life control, and general activity subscales of the Multidimensional Pain Inventory showed significant improvement from admission to dismissal (all $P < .05$). Similarly, the scores of the Pain Catastrophizing Scale, the Center for Epidemiologic Studies Depression Scale, and the physical functioning and emotional role limitation subscales of the 36-Item Short Form Health Survey were significantly improved after intervention (all $P < .01$).

Conclusion: The results of our study indicate that pain rehabilitation is a useful method for managing pain-related impairment in physical and emotional functioning in patients with erythromelalgia.

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ERYTHROMELALGIA IS A RARE clinical syndrome of uncertain cause, with marked heterogeneity of the affected population.[1] It is characterized by the triad of pain, redness, and elevated temperature, usually in the extremities. The onset may be gradual, with some cases remaining mild and unchanged for decades, or it may begin quickly, spreading or becoming disabling within months. Morbidity and mortality in patients with erythromelalgia are higher than in the general population of the United States.[2]

The pathophysiology of erythromelalgia is not clearly understood; however, the underlying pathologic mechanisms most likely involve complex dysregulation of cutaneous blood flow that ultimately results in microvascular ischemia. Determining the nature of this dysregulation has been challenging because control of cutaneous blood flow depends on an intricate interplay of systemic and local signals.[1] However, it is likely that a small-fiber neuropathy contributes to this dysregulation.[3,4]

In the familial form, erythromelalgia is inherited in an autosomal dominant fashion and is caused by missense mutations in the *SCN9A* (OMIM 603415) gene.[5,6] This gene is known to encode a voltage-gated sodium channel α-subunit, $Na_v1.7$.[5] The $Na_v1.7$ channel is preferentially expressed on nociceptive dorsal root ganglion and sympathetic ganglion neurons.[7] Expression of this sodium channel also is increased in dorsal root ganglia under inflammatory conditions.[8] The mutation of $Na_v1.7$ lowers the threshold for single action potentials and for high-frequency firing in dorsal root ganglia.[5] Thus, current research seems to support the theory that the hyperexcitability in nociceptive dorsal root ganglia as a result of mutant $Na_v1.7$ channels contributes to the pathophysiology of this painful neuropathy.[5]

Symptomatic improvement is the purpose of pharmacologic treatment of erythromelalgia. Most patients with this diagnosis are subjected to polypharmacy in an attempt to manage pain if it is so severe that it interferes with activities of daily living.[9] Medications such as opioids, gabapentin, lidocaine patches, benzodiazepines, and nonsteroidal anti-inflammatory drugs (NSAIDs) are used frequently; however, in most cases, these treatments either have no proven efficacy or provide only limited relief.[9] No single drug group, medication, or method of treatment is universally helpful for relief of symptoms.[2] Therefore, the ideal therapeutic approach to managing erythromelalgia is yet to be defined.[9,10]

Cohen[9] concluded that because of the variable response to management with medication, careful trial and error should be used in each case to provide the most benefit. In most cases over the years, management of erythromelalgia has included pharmacotherapy, patient education, learning to avoid episodes, relieving the discomfort of episodes, and controlling secondary and underlying factors.[10]

Multidisciplinary pain rehabilitation is a well-characterized outpatient treatment of chronic pain from diverse causes.[11] Because patients with chronic pain frequently have decreased emotional and physical functioning, the primary treatment goal of pain rehabilitation is restoration of functioning. In general, a cognitive-behavioral therapy model serves as the basis for treatment and incorporates stress management, relaxation training, physical reconditioning, chemical health education, activity moderation, and elimination of pain-inducing behaviors.[11] Patients undergoing pain rehabilitation receive daily physical and occupational therapy and attend daily educational group sessions related to the adverse effects of chronic pain on functional ability. At our institution, multidisciplinary pain rehabilitation incorporates withdrawal or tapering of NSAIDs, muscle relaxants, benzodiazepines, and opioid analgesic medications[12] because these medications have no proven efficacy and provide limited symptomatic benefits. Withdrawing these drugs also eliminates drug-related adverse effects and the risk of medication-related complications.

To our knowledge, the use of multidisciplinary pain rehabilitation for treatment of chronic pain-related impairment in functional ability in patients with erythromelalgia has not been previously reported. The purpose of this retrospective case series was to describe the immediate posttreatment outcomes in patients with erythromelalgia undergoing multidisciplinary pain rehabilitation.

METHODS

PATIENTS

Our retrospective case series included 9 patients with a diagnosis of erythromelalgia admitted to the Mayo Clinic Comprehensive Pain Rehabilitation Center, Rochester, Minnesota, from January 1, 2002, through June 30, 2007. The study protocol was approved by the Mayo Clinic Institutional Review Board.

Relevant clinical data collected included age, marital status, state of residence, duration of illness, educational achievement level, and medication use at admission and dismissal. In addition, at admission and dismissal, patients completed 4 standardized questionnaires (Multidimensional Pain Inventory [MPI], 36-Itam Short Form Health Survey [SF-36], Pain Catastrophizing Scale [PCS], and Center for Epidemiologic Studies Depression Scale [CES-D]) to assess and quantify pain severity, perceived life control, affective distress, pain catastrophizing, life interference because of pain, and physical and emotional health attributes.

PAIN REHABILITATION PROGRAM

The outpatient pain rehabilitation program is of 3 weeks' duration. The primary goal of treatment is restoration of functional ability. In general, patients eligible for admission to the program have persistent noncancer-related pain and associated functional impairment. Before admission, all patients were receiving medical care from a physician and had incomplete symptomatic relief from interventional pain procedures, multiple pharmacologic trials, or repeated courses of physical therapy. Admission to the rehabilitation program is on a revolving basis, and patients attend the program 8 hours daily for 15 consecutive working days.

A secondary treatment goal is discontinuation or reduction in the use of NSAIDS, muscle relaxants, benzodiazepines, and opioid analgesic medications. Tapering of all medication is initiated and coordinated by a physician after admission to the rehabilitation program. After medication discontinuation in this study, no other analgesic medications were given. Daily opioid intake at admission was changed to oral morphine equivalents, consistent with our established methods for analyzing opioid use.

MULTIDIMENSIONAL PAIN INVENTORY

The MPI is widely used to assess and quantify the psychosocial effects of chronic pain.[13] This 52-item self-report questionnaire contains 12 subscales, and responses to each item are scored by the patient on a 7-point Likert scale. The MPI has proven reliability and construct validity.[14] The raw scores are converted to standardized T scores with a range of 0 to 100.[15] Four MPI subscales were used for this study: pain severity, perceived life control, general activity, and life interference because of pain. The pain severity subscale quantifies pain intensity and pain-related suffering, the perceived life control subscale is a measure of problem management and overall coping skills, the general activity subscale assesses participation in home tasks and social activities, and the life interference subscale assesses the interference of pain in relationships and daily activities. Lower scores on the pain severity and life interference subscales indicate less psychologic impairment. Conversely, higher scores on the life control and general activity subscales are desirable and indicate less psychosocial impairment.

SF-36 STATUS

The SF-36 was developed for use in clinical practice and research to assess a patient's physical and emotional health attributes during the last month.[16] The self-administered 36-item questionnaire contains items scored on 2-, 3-, 5-, or 6-point Likert scales. The raw scores are converted to T scores with a normative value of 50 and an SD of 10 for each of the subscales. Standardized T scores were calculated by using published age- and sex-specific mean scores and standard deviations for the SF-36 scales in the general US population.[17] Higher

Table. Results of Standardized Patient Questionnaires

Scale/Subscale	Questionnaire Scores, Mean (SD)			*P* Value
	Admission Score (n=8)	Dismissal Score (n=7)	Score Difference (n=7)	
MPI				
Pain severity	51.1 (9.1)	40.9 (14.3)	−10.2 (13.3)	.09
Life interference	52.5 (8.7)	39.7 (11.7)	−12.9 (13.5)	.045
Life control	49.1 (7.8)	57.3 (4.3)	8.14 (8.6)	.046
General activity	46.6 (4.2)	54.0 (7.4)	7.5 (7.9)	.047
SF-36				
Health perception	34.7 (15.3)	41.8 (13.4)	7.0 (12.0)	.17
Physical functioning	20.1 (13.6)	42.8 (9.0)	22.7 (13.9)	.005
Role limitation, physical	28.8 (12.6)	38.6 (14.3)	9.7 (16.0)	.16
Role limitation, emotional	30.8 (9.8)	50.3 (7.3)	19.5 (13.3)	.008
PCS				
Depressive symptoms	29.9 (6.8)	14.7 (8.9)	−15.1 (8.2)	.003
CES-D				
Depressive symptoms	27.1 (8.6)	10.4 (7.9)	−16.7 (11.7)	.009

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; MPI, Multidimensional Pain Inventory; PCS, Pain Catastrophizing Scale; SF-36, 36-Item Short Form 36 Health Survey.

scores reflect a more favorable health status. Four of the subscales were used for this study: health perception, physical functioning, role limitations from emotional problems, and role limitations from physical problems. High scores on the health perception subscale reflect a belief that personal health is excellent. Persons involved in vigorous physical activities would score high on the physical functioning subscale.[17-19] Similarly, those who are able to work and perform other daily activities without limitations because of physical or emotional problems would score high on both the physical and emotional role limitations subscales.

PAIN CATASTROPHIZING SCALE

The PCS comprises 13 items scored on a Likert scale from 0 (not at all) to 4 (all the time).[20] A total PCS score of 30 corresponds to the 75th percentile of the distribution of PCS scores in clinical samples in patients with chronic pain. Pain catastrophizing has been broadly described as an exaggerated negative mental set associated with actual or anticipated pain experiences.[21]

CENTER FOR EPIDEMIOLOGIC STUDIES DEPRESSION SCALE

The CES-D[22] provides a measure of depressive symptoms that have occurred in the last week. Four factors compose the composite CES-D score: measures of general depressive and somatic symptoms, positive affect, and interpersonal difficulties. The 20-item self-administered questionnaire has established reliability and validity and is scored on a 4-point Likert scale. Total scores range from 0 to 60; higher scores indicate greater levels of depression. A cutoff score of 16 or higher has been used to identify patients with minor depressive symptoms,[23] and a score of 27 or higher has been used to identify major depression in patients with chronic pain.[24]

STATISTICAL ANALYSIS

The difference in the mean scores from admission and dismissal for the MPI, SF-36, PCS, and CES-D questionnaires were compared using 2-sided paired *t* tests. The level of significance for all statistical tests was $P < .05$.

RESULTS

Nine patients with erythromelalgia were admitted to the pain rehabilitation program during the study; 7 patients completed the program. One patient terminated participation 4 hours after admission; no clinical data were available for this patient because he did not complete the survey required at the initiation of rehabilitation. Another patient completed 10 days of the program and believed he had received adequate instruction to manage his pain, and he chose to voluntarily withdraw. Therefore, admission clinical data were available for 8 patients, and immediate posttreatment outcomes were available for 7 patients.

Eight patients were admitted to the program with a diagnosis of erythromelalgia. Seven of the 8 patients were women (87.5%), all were white, 4 (50.0%) were married, and 4 (50.0%) were residents of Minnesota. Their mean (SD) age was 43.1 (16.8) years (age range, 21-74 years). The group was educated, with a mean (SD) of 14.1 (2.3) years of education, although most (6 patients [75.0%]) were not working. Patients had pain from erythromelalgia for a mean (SD) of 4.9 (3.0) years (range, 8 months to 8.8 years). Five patients (62.5%) were taking opioid analgesic medications at admission. The mean (SD) daily morphine equivalent dose was 185.3 mg/d (260.4 mg/d) (range, 11-630 mg/d). At dismissal, only 1 patient was still using opioids, but the morphine equivalent dose was decreased from 630 mg/d at admission to 390 mg/d at dismissal. Similarly, 5 patients were receiving NSAIDs and 5 were receiving benzodiazepines at admission. At dismissal, 4 patients were receiving NSAIDs and 3 continued to receive benzodiazepines. Seven patients (87.5%) completed the treatment program.

The **Table** gives the admission and dismissal subscale scores from the MPI. After completion of the rehabilitation program, patients reported significant improvement in life control ($P = .046$) and general activity ($P = .047$). Similarly, life interference because of pain was significantly decreased at dismissal ($P = .045$). Although

the MPI pain severity subscale score decreased, the change was not statistically significant ($P = .09$).

Analyses of the admission and dismissal subscale scores from the SF-36 (Table) showed significant improvement in physical functioning ($P = .005$) and emotional role limitation ($P = .008$). At admission, the mean physical functioning subscale score was 3 SDs below the mean for the general US population. Similarly, the mean role limitation subscale scores and the mean health perception score were 2 SDs and 1 SD, respectively, below the mean for the US population. At dismissal, the mean physical functioning and emotional role limitation scores improved by 2 SDs, whereas the mean general health perception and physical role limitation scores improved by almost 1 SD.

The Table also lists the mean admission and dismissal scores from the PCS and CES-D scales. The mean change on both scales indicated significant decreases in depressive symptoms and negative pain-related cognitions.

COMMENT

The results of the present study show that pain-related impairment in emotional and physical functioning improves in patients with erythromelalgia after multidisciplinary pain rehabilitation. Specifically, immediate posttreatment measures of depression, life control, life interference, physical functioning, general activity, emotional limitation, and pain catastrophizing improved significantly. To our knowledge, this is the first study to describe the use of multidisciplinary pain rehabilitation for management of chronic pain–related functional impairment in patients with erythromelalgia.

The dismissal scores for the MPI showed a significant decrease in the life interference score ($P < .05$) and significant increases in the life control and general activity scores ($P < .05$) compared with the admission scores. Although the difference in pain severity score was not statistically significant, pain severity was still decreased after the intervention. The goal of the comprehensive pain rehabilitation program is to restore functional ability and improve quality of life, not necessarily to decrease pain severity. From our results for the MPI, it is evident that the rehabilitation program provides means for the patient to learn to cope with chronic pain and gain a better quality of life.

The SF-36 measure increased for all subscale measures (physical functioning, general health perception, physical role limitation, and emotional role limitation) at dismissal compared with admission. The higher scores reflect greater functioning and a more favorable health status in our study population. The changes in physical functioning and emotional role limitation were both statistically significant ($P < .01$).

Significant changes also were demonstrated on the CES-D scale ($P < .05$) and the PCS ($P < .05$). Fewer patients had symptoms of depression at dismissal than at admission. Pain catastrophizing is one of the most important psychologic predictors of a patient experiencing pain. It has been shown to be associated with longer hospital stay, increased disability, increased pain behavior, greater use of health care services, and use of analgesic medications. The definitive role of this outcome measure in chronic pain syndromes emphasizes the importance of the significant decrease in the PCS score in our study of patients with erythromelalgia.

Although restoring patient functioning and improving quality of life are the main focuses of the pain rehabilitation program, another important goal of the program is to decrease or eliminate the use of opioids for treatment of pain. Our study results showed a decrease in the number of patients using opioids to manage pain (n = 1) at dismissal from the pain rehabilitation program vs patients using opioids at admission (n = 5). Despite discontinuing the use of opioids, pain severity measured using the MPI was still lower at dismissal than at admission. For the 1 patient who continued to receive opioid medication, the dosage was decreased from 630 mg/d at admission to 390 mg/d at dismissal. This result further attests to the benefit of the pain rehabilitation program in our patients and shows that opioids can be withdrawn from patients with erythromelalgia without adversely affecting posttreatment outcomes. We did not investigate the long-term effects of withdrawing opioid medication.

Various approaches to managing the symptoms of erythromelalgia have been described. The Erythromelalgia Association has reported some success with topical treatment such as capsaicin and oral medication such as aspirin, gabapentin, misoprostol, anticonvulsants, calcium antagonists, tricyclic antidepressants, and serotonin-reuptake inhibitors .[9,25-27] However, many patients have resorted to polypharmacy because no single drug has been universally helpful in alleviating symptoms. Some parenteral approaches to the management of erythromelalgia also have been reported.[9] Lidocaine infusions elicited a 90% decrease in pain and modest alleviation of redness in a man with long-term severe erythromelalgia.[28] Other parenteral approaches include nitroprusside infusions and prostaglandin infusions.[9] In severe cases, invasive procedures have been reported such as sympathetic blockade and epidural injection, sympathectomy, dorsal column stimulation, and, in a case report from Russia, neurosurgery.[29] An approach to managing erythromelalgia nonmedicinally was reported in a study by Putt[30] in which 1 patient reported pain reduction by using biofeedback. A survey of members of the Erythromelalgia Association reported by Cohen[9] noted that 2 of 4 patients benefited from biofeedback. This certainly emphasizes that, in attempting to alleviate the debilitating symptoms of erythromelalgia, physicians should consider nonconventional methods of management to yield better outcomes in patients with erythromelalgia.

Although no previous reports have described the efficacy of a pain rehabilitation program in managing the symptoms of erythromelalgia, our study can be compared with previous studies that showed successful management of chronic noncancer pain with pain rehabilitation. Rome et al[31] showed significant improvement from admission to discharge for all of the outcome variables assessed in patients receiving treatment at the

pain rehabilitation center for management of chronic noncancer pain; our results with erythromelalgia patients were similar. In addition, a study by Hooten et al[12] showed significant improvement ($P<.001$) in treatment outcomes after pain rehabilitation in patients with fibromyalgia. These 2 studies[12,31] also showed significant decreases in depressive symptoms (CES-D scale) and negative pain-related cognition (PCS scale), as was the case in our study.

The efficacy of pain rehabilitation has been well established.[32-34] Our study extends previous knowledge by showing that the benefits of pain rehabilitation are obtained not only in patients with common chronic noncancer pain such as headache, low back pain, and fibromyalgia but also in patients with other pain syndromes such as the rare clinical syndrome of erythromelalgia.

One limitation of our study is that it is a retrospective analysis of a rare, poorly defined clinical syndrome at a tertiary referral center. The study was subject to recall bias because questionnaires were used. In addition, the results may reflect, in part, Berkson bias because patients coming to our tertiary referral center are more likely to have more than 1 medical problem. In addition, all patients were referred to the comprehensive pain rehabilitation pain program, after which patients were self-selected and had the health care resources and motivation to participate in a daily 3-week outpatient rehabilitation program. Furthermore, patients in the study were predominantly women, were highly educated, and, most important, had a long-standing history of pain. As a result of this selection bias, the study results may not be applicable to all patients with erythromelalgia. Another limitation of the present study is the absence of long-term treatment outcome data. Although the immediate posttreatment results are favorable, observation over an extended period is necessary to firmly define the efficacy of a pain rehabilitation program in patients with erythromelalgia.

The symptoms of erythromelalgia are difficult to treat and are not fully responsive to any one medical intervention. Although patients with erythromelalgia use various medications, the therapeutic benefits are often limited and overall patient satisfaction is low. The therapeutic benefits of comprehensive pain rehabilitation have been demonstrated; however, our findings emphasize the need for further clinical and basic science research to determine the physiologic and psychologic mechanisms that mediate the effects of comprehensive pain rehabilitation.

An understanding of alternate methods of managing erythromelalgia is important because of the devastating symptoms and because the diagnosis is associated with significantly decreased scores in almost all health domains and with a significant decrease in survival. In conclusion, physicians should consider a comprehensive pain rehabilitation program for patients in whom the conventional forms of medical therapy for erythromelalgia have not been beneficial.

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