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Article *in* Orthopedics · March 2014

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Allergy/Hypersensitivity Reactions as a Predisposing Factor to Complex Regional Pain Syndrome I in Orthopedic Patients

XINNING LI, MD; KEITH KENTER, MD; ASHLEY NEWMAN, BS; STEPHEN O'BRIEN, MD, MBA

abstract

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Several predisposing conditions have been associated with complex regional pain syndrome I (CRPS I). The purpose of this study was to determine the relationship between a history of allergy/hypersensitivity reactions and CRPS I in orthopedic patients. Orthopedic patients with CRPS I (n=115) who experienced pain relief after a successful sympathetic nerve blockade were identified for study inclusion; a control group (n=115) matched to the CRPS I group by age, sex, and location of injury was also included. All patients in the study had an average age of 42 years. In the CRPS I group, all participants were Caucasian and the majority (80.8%) were women. The skin of patients with CRPS I was described as fair (57.7%), mottled (57.7%), or sensitive (80.8%). Of the patients with CRPS I, 78 (67.8%) reported a statistically significant history of allergies compared with the 39 (33.9%) patients in the control group ($P<.0001$). Patients with CRPS I who experienced complete pain relief for at least 1 month following a single sympathetic nerve block were asked to answer a questionnaire (n=35), and some then underwent immediate hypersensitivity testing using a skin puncture technique (n=26). Skin hypersensitivity testing yielded an 83.3% positive predictive value with an accuracy of 76.9%. Based on these results, a positive history for allergy/hypersensitivity reactions is a predisposing condition for CRPS I in this subset of orthopedic patients. These hypersensitivity reactions may prove important in gaining a better understanding in the pathophysiology of CRPS I as a regional pain syndrome.

The authors are from the Department of Orthopaedic Surgery (XL), Boston University School of Medicine, Boston, Massachusetts; the Department of Orthopaedic Surgery (KK), University of Cincinnati Medical School, Cincinnati, Ohio; and the Department of Orthopedic Surgery (AN, SO), Hospital for Special Surgery, New York, New York.

The authors have no relevant financial relationships to disclose.

Funding was provided internally by the Hospital for Special Surgery.

Correspondence should be addressed to: Xinning Li, MD, Department of Orthopaedic Surgery, Boston University School of Medicine, 720 Harrison Ave, Boston, MA 02118 (xinning.li@gmail.com).

Received: August 15, 2013; Accepted: October 9, 2013; Posted: March 11, 2014.

doi: 10.3928/01477447-20140225-62

During the American Civil War, 3 U.S. Army surgeons documented 11 soldiers with allodynia and hyperalgesia of their affected limbs following gunshot wounds involving nerve injury.[1,2] These surgeons, S. W. Mitchell, G. R. Morehouse, and W. W. Keen, described temperature and skin changes in the extremities of some of the soldiers and developed the term erythromelalgia but later called this painful condition causalgia.[3] Over time, others have noticed similar clinical features but have submitted their findings using different terminology.[4-10] Because of the association between the painful symptoms and the dysfunction of the autonomic nervous system, manifested by cutaneous changes, Bonica[11] popularized the term reflex sympathetic dystrophy (RSD).

The American Association for Hand Surgery has clinically defined RSD as "a pain syndrome in which the pain is accompanied by loss of function and evidence of autonomic dysfunction."[12] Major nerve injury is not mentioned in this ad hoc committee's report, adding to the confusion of terminology and pathophysiology. More recently, dissatisfaction with the term RSD has occurred because not all of the cases seem to have sympathetically maintained pain and not all have been dystrophic in nature. Therefore, the International Association for the Study of Pain taxonomy has revised the term RSD to complex regional pain syndrome (CRPS).[9,13] Under this classification scheme, RSD is now referred to a CRPS type I and causalgia with evidence of nerve damage is now referred to as CRPS type II. The authors believe that RSD, or CRPS I, is a nonconclusive term describing the abnormal hyperactivity of the autonomic nervous system with a wide spectrum of clinical presentations. It usually occurs following a physical injury or surgery, but spontaneous onset has also been reported.[14] Disease course varies significantly from mild and self-limiting symptoms to severe disabling chronic symptoms that will place significant limitations on a patient's activities of daily living.

The spectrum of clinical presentations coupled with changing taxonomy makes understanding pain syndromes difficult. O'Brien et al[15] emphasized the importance of establishing a precise diagnosis as the source of pain before contemplating any surgical intervention in patients with CRPS of the knee. It was also observed by this team that many of these patients with CRPS had an increased history of allergic reactions.[15] Because adrenergic medications can be effective in the treatment of some allergy/hypersensitivity reactions and adrenergic mediated responses dominate signaling within the sympathetic nervous system, the current authors hypothesize that an underlying adrenergic hypersensitivity may be the cause of both hypersensitivity reactions and CRPS in some patients. Considering only the relationship between allergy/hypersensitivity and CRPS, it is possible that the adrenergic system in these patients may be inherently skewed to be more reactive. Following this logic, many patients with CRPS I should have an increased history of allergic or hypersensitivity reactions compared with patients without any history of pain syndromes.

The purposes of the current study are to determine whether this relationship does exist in patients presenting to an orthopedic clinic with CRPS I and whether this relationship is statistically different from a similar matched group of patients without CRPS I.

Materials and Methods

One hundred fifteen orthopedic patients with a diagnosis of CRPS I were retrospectively reviewed. The diagnosis of CRPS I was determined based on the following: pain out of proportion to the physical findings, vasomotor disturbances seen by physical findings, and a positive response to diagnostic sympathetic nerve blockade. All patients were under the primary care of the senior author (S.O.).[16] A sympathetic nerve blockade was administered to all patients by board-certified attending anesthesiologists specializing in pain management and performed as previously described.[15] A positive nerve block response was defined as either partial or complete alleviation of pain. Follow-up to therapy was documented jointly by the anesthesia pain service and the senior author.

For comparison purposes, 115 randomly selected orthopedic patients with no history of pain syndromes were also reviewed. These patients were also under the primary care of the senior author for orthopedic conditions unrelated to CRPS I. This group of patients acted as the control group and was matched to the CRPS I group by age, sex, and injury location. All patients completed a questionnaire developed by the Allergy and Immunology Division at the authors' institution.

To confirm a history of allergy/hypersensitivity reactions, patients underwent skin allergy testing. To avoid skewing the data, it was decided to include only the CRPS I patients who had complete alleviation of their pain for at least 1 month after a single sympathetic nerve blockade. Immediate hypersensitivity skin testing was administered by a trained, board certified, allergist using the skin prick puncture method with a commercially available multitest device. After approval by the authors' Institutional Review Board and informed consent from patients were obtained for the procedure, patients underwent immediate hypersensitivity skin testing.

The skin of the forearm was cleansed with 70% isopropyl alcohol and allowed to dry. Aseptically, the multitest applicator device containing the allergic solutions, histamine, and normal saline was placed on the arm and pressed into the skin firmly with a side-to-side rocking motion, resulting in an intradermal introduction of the allergen, histamine, and normal saline control to individual sites. Fifteen to 20 minutes after the skin was injected, each

test site was observed for erythema or wheal formation, with those measuring 3 mm or larger than the histamine control considered a positive test. After the tests were recorded, the forearm was washed with water to remove all allergens.

Using this methodology, the multitest applicator device contained 50% glycerosaline (negative control), histamine (1:1000) (positive control), and the following allergens: (1) Environmental Inhalants I: house dust (1:10), *Dermatophagoides farineae* (10.000 AU/cc), *D pteron* (10.000 AC/cc), cockroach (1:10); (2) Environmental Inhalants II: cat epithelium (1:10); (3) Seasonal Screens: ragweed (tall and short) (1:20); and (4) Molds: Alternaria tenuis (1:10), *Aspergillus fumigatus* (1:10). To prevent false-negatives, all patients were asked to refrain from taking all antihistamine medication 24 hours before skin testing; hydroxyzine, tricyclic antidepressants, terfenadine, and loratadine beginning 96 hours before skin testing; and astemizole beginning 4 weeks or longer before skin testing. Statistical significance was measured by Fisher exact test with a *P* value of .05 or less.

Results

In total, 115 patients in each group were reviewed. Average age of all 230 patients was 42 years. The youngest patient treated in the patient population with CRPS I was a girl aged 17 years. In the CRPS I group, the majority (80.8%) of patients were women and all patients were Caucasian. The lower extremity was involved in 82.2% of patients from CRPS I.

One hundred fifteen patients had pain out of proportion with their observed physical findings, cutaneous vasomotor disturbances, and at least 1 positive response to a diagnostic sympathetic nerve block. These patients were considered to have a working diagnosis of CRPS I. Based on the questionnaire, 78 (67.8%) patients reported a history of allergy/hypersensitivity reactions. This was compared with the 39 (33.9%) patients in the control group who reported an allergy/hypersensitivity history and was found to be statistically significant (*P*<.0001).

All patients with CRPS I were evaluated more critically based on their response to the sympathetic nerve blocks. All patients had successful sympathetic blocks defined by an increase in skin temperature of the affected limb with a concomitant increase in pulse-wave plethysmography. In this evaluation, 35 patients had complete relief of their pain after 1 block, 68 patients experienced partial pain relief after 1 block or complete pain relief after several blocks, and 12 patients had no long-term pain relief after multiple, successfully placed sympathetic nerve blocks. No complications resulted from the sympathetic nerve blocks. All 35 patients with complete alleviation of their pain after 1 sympathetic nerve blockade answered the questionnaire. Nine of these patients refused immediate hypersensitivity testing by skin puncture and were not included in the demographic data. The remaining 26 patients underwent immediate hypersensitivity skin testing.

Table 1 summarizes the demographic data for the 26 patients with a diagnosis of CRPS I who had complete alleviation of pain for at least 1 month following a single sympathetic nerve block and underwent the skin testing. Average age in this subgroup of patients was 40 years (range, 26-56 years). There were 21 (80.8%) women and 5 (19.2%) men. The majority (n=22; 84.6%) of injuries were located in the lower extremities of these patients. All patients were Caucasian. The patients' skin was described as fair (n=15; 57.7%), mottled (n=15; 57.7%), or sensitive (n=21; 80.8%) before testing. When reviewing the questionnaires that identified other hypersensitive or autoimmune type diseases, 16 (61.5%) patients had been diagnosed with adult onset asthma, most of whom required some sort of treatment in the past by their primary care physicians. An additional 4 patients had a family member who had been diagnosed with asthma.

Table 1

Demographic Data for Patients With CRPS I (n=26)

Demographic	Value
Average age, y (range)	40 (26-56)
Sex, No. (%)	
Female	21 (80.8)
Male	5 (19.2)
Extremity	
Upper	4 (15.4)
Lower	22 (84.8)
Skin description, No. (%)	
Fair	15 (57.7)
Mottled	15 (57.7)
Sensitive	21 (80.8)
Asthma	16 (61.5)
Raynaud's phenomenon	1 (3.8)
Rheumatoid arthritis	1 (3.8)
Systemic lupus erythematosus	0
Diabetes mellitus	1 (3.8)
Other disease, No. (%)	16 (61.5)
Family member with CRPS I	3 (11.5)

All 26 patients tolerated the hypersensitivity skin puncture testing with no complications. **Table 2** summarizes the results of the 26 patients who underwent the skin puncture testing. Twenty patients demonstrated a positive confirmatory result when comparing their skin puncture tests with their allergic reaction history. Six patients demonstrated a nonconfirmatory result when comparing their skin puncture tests to their allergic reaction history; 3 of these patients had no skin reactions to the tested allergens despite their report of a history of allergic reactions. The remaining 3 patients had positive skin puncture tests but reported no significant history of allergies. This gives the current test results an 83.3% positive predictive value with an accuracy of 76.9%.

Table 2
Skin Reactions Compared with Patient Allergy History

History	Positive Skin Test, No.	Negative Skin Test, No.
Positive	15	3
Negative	3	5

Twenty-five of the 26 patients reacted to the histamine. The patient who did not react to the histamine also demonstrated no reactions to any of the other tested allergens. Specific questioning revealed that this patient was taking several antihistamine medications and had been treated for multiple allergies since childhood. The patient also revealed that she had previously undergone a skin puncture test by her allergist, who documented significant hypersensitivity reactions to several allergens included in the current study. This outside report is considered confirmatory for her history of allergic reactions. Interestingly, of the 35 patients who had complete alleviation of their pain after 1 sympathetic block, 3 reported having a family member with CRPS I. All 3 patients' family members were first-generation relatives (2 mothers and 1 daughter). The CRPS I had developed in 2 of these patients following minor trauma and in another patient after elective surgery.

Discussion

This study aims to identify specific demographics that may represent common findings in orthopedic patients with a diagnosis of CRPS I. The inability to quantitatively measure pain in this subset of patients with pain syndromes who also present with orthopedic issues can lead to a poor understanding of the patient's clinical complaints and thus a breakdown in the patient-physician relationship. Furthermore, the report of multiple allergic reactions given by a patient could mislead the physician into thinking the patient was emotionally unstable. The current authors have described evidenced-based findings that support a strong correlation between allergy and CRPS I. These allergic and hypersensitivity reactions may prove important in developing a better understanding of the pathophysiology of CRPS.

Since Mitchell's original description of causalgia,[1,2] many authors have attempted to explain the characteristic burning and associated clinical findings seen in patients with pain syndromes. Some believe the disease process is due to dysfunctional peripheral nerves,[18,19] whereas others report the pathophysiology is in the soft tissues.[19] Others believe that the central nervous system is the region of concern.[20] The simple hypothesis by Livingston[18] of a "vicious circle" postulates that peripheral stimulation of nociceptors reflexively stimulate an increased response from the efferent sympathetic system. This increased top-down activity results in vasoconstriction, intensifying the nociceptors stimulation and amplifying pain.[21] Doupe et al[17] believed that artificial synapses could short circuit the peripheral sympathetic nerve fibers following tissue injury. Efferent sympathetic signals can be directly transmitted to sensory fibers, thus lowering their threshold for stimulation. Ecker[22] proposed that the problem may yield from an abundance of norepinephrine in the circulations of in patients with CRPS. Currently, it is still unknown whether CRPS pathophysiology involves systemic or local inflammation factors, microcirculation constriction, dysfunction of peripheral nerve structures or conduction, local tissue factors within the soft tissue, or a combination of some or all of the above factors.

The incidence of CRPS ranges from 5.46 to 26.2 per 100,000 person-years.[23,24] De Mos et al[24] reported that the most common precipitating event is a bone fracture, the average age of onset of 52 years, and the majority of instances occur in women. The variable nature of CRPS presentation makes the diagnosis difficult. Physician awareness of its existence and inclusion in the differential in a patient who presents with pain out of proportion with the physical findings are paramount. Several predisposing conditions associated with pain syndromes have been described.[8,13,25] Knowledge of these conditions can assist the treating physician in making an earlier diagnosis of CRPS. The current authors have described demographic data that may be useful in identifying a population of patients at risk for developing CRPS following an injury or surgery.

The current patients with CRPS I included a high percentage of women (80.8%) and patients with an average age of 40 years. Several authors have also reported similar demographic findings.[15,23,24] Other demographic findings demonstrated in the current CRPS patient population included fair (57.7%), mottled (57.7%), and sensitive (80.8%) skin and all patients were Caucasian. The majority of orthopedic patients in the current study also localized their initial injuries to the lower extremities. Historically, much of orthopedists' understanding regarding CRPS I has come from literature describing the pain syndrome in the upper extremity. The results of the current study have expanded this understanding to the lower extremity, especially to the knee following anterior cruciate ligament surgery or meniscectomy. The current authors believe that this extension has provided a better understanding of the pathophysiology of many pain syndromes.[15] It should also be noted that it is possible that the findings in this study may be biased by sample selection. However, due to the congruency the current results have with

existing literature, the authors believe that this bias is at a minimum.

In the current study, 67.8% of all patients with CRPS I reported some type of history with allergic reactions. This result is statistically significant when compared with the control group ($P<.001$). The control group was randomly selected but matched to the patients with CRPS I by age, sex, and injury. The authors believe that the control group represents the typical patient population seen in a general orthopedic surgery practice. Of the control group, 33.9% reported a history of allergic reactions. This number is representative of the amount of allergies reported in the general population.[26]

To strengthen the current results, the authors believed it was important to stratify the group of CRPS I patients who had a single sympathetic nerve block that alleviated all pain symptoms for at least 1 month; again, a high percentage of these patients reported a history of allergies (69.2%). By testing the patient's history of allergies using immediate hypersensitivity skin tests, the authors found a high positive predictive value (83.3%) with an accuracy of 76.9%. Interestingly, 3 patients in this group were found to have positive immediate hypersensitivity reactions using a skin puncture technique but reported no history of allergic reactions. This finding may represent an increased sensitivity to circulating catecholamines or other paracrine mediators found in immediate hypersensitivity reactions. If there is an increased sensitivity or responsiveness of the vascular adrenergic receptors in patients who develop immediate hypersensitivity reactions, then this could also explain the allodynia and hyperalgesia seen in patients with pain syndromes.

Recently, experimental findings suggest that hypersensitive sympathetic adrenergic receptors may be related to the generation of the vascular abnormalities that has also been observed in patients with different pain syndromes. Abnormalities in the rhythmic cycling of cutaneous blood flow have been documented in patients with CRPS.[27] Drummond et al[28] suggested that patients with CRPS have super sensitivities to the sympathetic catecholamines. More recently, direct in vivo evidence has been documented for increased responsiveness of venous alpha-adrenergic receptors to locally infused norepinephrine in the extremities of patients with CRPS.[29] However, this correlation warrants further investigation.

The mainstay in the treatment of CRPS is early diagnosis, early pain control, and early mobilization through physical therapy. The most effective form of treatment is interpretation of the sympathetic arc. This can be accomplished with anesthetics by stellate ganglion blockade for upper extremity involvement or by lumbar sympathetic chain blockade for lower extremity involvement. Adrenergic receptor blocking medications, such as phenoxybenzamine, and catecholamine depleting agents, such as guanethidine and reserpine, have been successful in treating patients with pain syndromes.[10,20,30,31] Likewise, it is well accepted that adrenergic medications are effective in treating hypersensitivity reactions, especially asthma. The blockade of beta2-adrenergic receptors will result in an increased sensitivity to bronchoconstriction agents, including the alpha2-adrenergic agents. When specifically questioning patients about other hypersensitivity and autoimmune diseases, 61.5% of the patients with CRPS I who had a successful single sympathetic nerve blockage also reported a diagnosis of adult-onset asthma. Most of these patients required some type of treatment for their asthma.

Previous reports have linked both migraines and asthma as predisposing factors in developing CRPS.[32] The underlying pathophysiology between migraines, asthma, and increased allergy/hypersensitivity may be related to neurogenic inflammation that is marked by peptides, such as substance P,[33] and calcitonin gene-related peptide.[32] Increased serum levels of substance P and calcitonin gene-related peptide have also been reported in patients with migraines and asthma,[34,35] which has been linked to patients with CRPS.[36-39] Furthermore, levels of both tumor necrosis factor alpha and interleukin-6 were at a significantly higher level in blisters found on the extremities of patients with CRPS compared with the patient's nonaffected side.[40-42] These 2 cytokines are products of mast cells, which are major effectors in allergic and hypersensitivity reactions,[43] and thus further support the connection between an increase in allergy/hypersensitivity in patients with CRPS. In contrast to the above, Wesseldijk et al[44] reported no significant difference in terms of allergy history in patients with CPRS vs control patients in a Dutch population. However, they did find a higher level of IgE (30%) in the serum of CRPS patients when compared with the general population that served as the control group.[44]

Conclusion

These findings suggest that a history of asthma and allergy/hypersensitivity reactions may be another predisposing factor in the development of CRPS I. These hypersensitivity reactions may prove important regarding a better understanding of the development of many pain syndromes that may present in orthopedic patients after injury or postoperatively. This can be helpful not only in the basic science understanding of CRPS, but also in the promotion of more specific and effective treatment modalities. Furthermore, it may also assist orthopedic surgeons in predicting what type of patients may have a higher risk of developing CRPS I during the pre- or postoperative period or following an injury or elective surgery.

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