National Institutes of Health Workshop: Reflex Sympathetic Dystrophy/Complex Regional Pain Syndromes—State-of-the-Science

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On December 15, 2001, the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Health Office of Rare Diseases convened a workshop on reflex sympathetic dystrophy (RSD)/complex regional pain syndromes (CRPS) chaired by Dr. Jon Levine, University of California-San Francisco (UCSF) and Dr. Cheryl Kitt (NINDS). The participants included neurologists, neuroscientists, patient advocates, and NINDS staff. The goal of the meeting was to bring together leading pain researchers to consider RSD/CRPS in the context of their own research paradigms, determine the state of the science, and identify new directions for research on this disorder.

Background

RSD, also known as CRPS Type I (here called RSD/CRPS), is a chronic condition characterized by burning pain and abnormalities in the sensory, motor, and autonomic nervous systems (1,2). The syndrome typically appears after an acute injury to a joint or limb, although it may occur with no obvious inciting event. In most cases, regardless of the site of injury, the symptoms begin and remain most intense in the distal extremity. In the initial stages of RSD/CRPS, pain and swelling from the injury do not subside but actually intensify (3), typically spreading from the site of the injury to other parts of the limb, to the contralateral limb, or to remote regions of the body. In affected areas, the skin and deep somatic tissues are painfully sensitive to touch, often red and abnormally warm because of alterations in regional blood flow (4–6). Changes in sweating patterns, hair growth, subcutaneous tissues, muscles, joints, or bones and difficulty moving the joint or limb are other hallmarks of the disorder. In addition to the evidence of inflammation (1) and abnormal autonomic nervous system function (5,7), there are changes in motor systems including tremor, weakness, and dystonia (8–14, cf., 15), which strongly suggest a significant causative central nervous system (CNS) component to the disease in at least a subgroup of patients. Although controversial, some authors have reported that, in a minority of patients, the syndrome may evolve through three stages (acute, dystrophic, atrophic), each marked by progressive pain and physical changes in the skin, muscles, joints, and bones. RSD/CRPS can affect both genders and all ages (including children), although it is thought to be more common between the ages of 40 and 60 yr and may be more frequent in women. The cause of RSD/CRPS is unknown, and current treatments are not effective for many patients (16).

Scientific Presentations

Experts from a wide variety of clinical and basic research areas, including neuroimaging, pain, neural plasticity, the sympathetic nervous system, and the immune system, were invited to bring their knowledge and research approaches to bear on the difficult
clinical problem of RSD/CRPS. The participants considered the current knowledge about RSD/CRPS in the context of the state-of-the-art research tools used in their laboratories and proposed ways to apply these approaches to RSD/CRPS. The goal of the conference was to foster innovative research into the mechanism(s), epidemiology, and treatment of RSD/CRPS by their cross-disciplinary discussions.

During their presentations, the participants suggested that the mechanism(s) that causes RSD/CRPS is elusive, primarily because of the number of complex systems affected. It became obvious that a single mechanism can barely account for all of the changes seen in patients with RSD/CRPS. Several innovative hypotheses were presented at the workshop and it was agreed that several mechanisms interact to produce the symptoms of RSD/CRPS.

- Drs. Ralf Baron and Wilfrid Jänig presented clear evidence of sympathetic nervous system dysfunction in their experimental studies of human patients with RSD/CRPS (6). Activating the sympathetic nervous system by lowering body temperature results in increased pain in the affected area in a subgroup of RSD/CRPS patients, whose pain is relieved by sympathetic nerve blockade [blockade of the sympathetic innervation to the affected area (4)]. This is clear evidence that the sympathetic nervous system is involved in generating and maintaining pain (spontaneous, mechanical allodynia) in RSD/CRPS patients who have sympathetically maintained pain (SMP) according to clinical criteria (17) and this is supported by experiments on RSD/CRPS patients using intracutaneous norepinephrine applications and control sympathetic blocks (18–20) as well as by a variety of animal experiments (21–27). However, this SMP mainly involves the deep somatic tissues! Although it is not known how autonomic dysfunction relates to the myriad tissue pathologies in RSD/CRPS, this evidence led the participants to generally agree on the following key issues: 1) RSD/CRPS is a neurological [rather than psychological (28)] disorder, and 2) RSD/CRPS is likely to be a disorder with both CNS and peripheral nervous system components (7,29–31).

- Dr. Clifford Woolf provided evidence that some types of neuropathic pain are related to changes in pain signaling pathways, including in the neurons of the spinal cord. Such modifications could distort the signaling process so that normally painless stimuli begin to produce pain, and stimuli that should be slightly discomforting actually produce severe, long-lasting pain. New technologies in gene and protein expression profiling should permit researchers to explore these issues further (32). However, it must be kept in mind that RSD/CRPS in most patients is triggered by trauma without obvious nerve lesions. Thus, the pain in these RSD/CRPS patients is not typical neuropathic pain as it is currently understood.

- Dr. Linda Watkins suggested that the immune system might have a role in the disorder because signs of inflammation (redness, swelling, increased blood flow, and tissue accumulation of immune cells) in the painful region are common in RSD/CRPS patients. The release of proinflammatory cytokines in response to neural and glial activation may be one connection between the abnormal regulation of the sympathetic nervous system and the characteristics of inflammatory immune reactions seen in the disorder (33,34). These thoughts connect to the idea that peripheral inflammatory processes are involved in the pathogenesis of early RSD/CRPS. However, the exact mechanisms of the initiation and maintenance of these inflammatory reactions, their connection to the sympathetic and afferent (peptidergic) innervation of the affected tissues, and their relation to the central changes (e.g., the spinal cord, as addressed by Dr. Watkins) are far from clear. Dr. Levine, who reviewed similarities between RSD/CRPS and autoimmune inflammatory diseases such as rheumatoid arthritis, provided support for this idea (35). He indicated furthermore that injury may trigger remote inflammatory responses and hyperalgesic behavior, both being possibly dependent on the sympathetic nervous system (36).

- Dr. Wilfrid Jänig approached the problem from a systems level and proposed that the abnormal integration of sensory, autonomic, and motor components at several levels in the CNS could be a cause of RSD/CRPS. According to this idea, the initial insult mostly occurs in the periphery and triggers changes in the central representations of the sensory, motor, and sympathetic systems which are reflected in the changes of the respective output systems observed in the RSD/CRPS patients. Subsequent interactions with the immune, endocrine, and vascular systems could lead to changes in the long-term responsiveness of the CNS that finally determines the disease symptomatology in the chronic state (7).

- Dr. Catherine Bushnell applied her expertise in neuroimaging to the question of nervous system activation in RSD/CRPS. She presented comparative brain imaging studies after cutaneous or visceral noxious stimuli to identify regions that are uniquely responsive to a particular type of painful stimulus (37). Similar comparisons between "normal" pain and pain in RSD/CRPS patients should help to clarify which regions of the nervous system are abnormally activated in this
disease state. This is a very attractive and promising idea in view of the finding that many chronic RSD/CRPS patients have generalized sensory deficits (cold, warm, pain, touch perception) that can be quantitated. If this is a CNS abnormality, functional imaging could suggest CNS sites that should be explored.

- Dr. Stephen Bruehl presented evidence that psychological distress in patients with CRPS is not a causative factor but might evolve secondary to the chronic pain syndrome. Furthermore, statistical factor analysis of multiple signs and symptoms in CRPS shows that the diagnostic criteria that have been defined so far should be extended by particular signs (e.g., by motor symptoms) to increase diagnostic sensitivity and specificity (1,36).

In summary, based on evidence from clinical observations, experimentation on humans, and experimentation on animals, the general hypothesis has been put forward that RSD/CRPS is a disease of the CNS. RSD/CRPS patients exhibit changes that occur in systems processing noxious, tactile, and thermal information, in sympathetic systems innervating blood vessels, sweat glands, and possibly other targets, and in the somatomotor system, indicating that the central representations of these systems are changed. The way these central changes are triggered by the peripheral trauma, which is often minor compared with the dramatic expression of the clinical phenomena, remains an enigma. Furthermore, how these central changes relate to the peripheral inflammatory/immune changes is entirely unclear. Finally, we cannot explain why pain and the other changes associated with the sympathetic nervous system (including swelling), the motor system, and the somatosensory system may disappear, in RSD/CRPS patients with SMP, after sympathetic blockade (e.g., with a local anesthetic or with guanethidine). It was agreed that, based on the clinical changes observed in the RSD/CRPS patients that can be measured quantitatively, it should be possible to formulate hypotheses about the underlying mechanisms. These hypotheses should be tested by using a multidisciplinary approach, which includes clinical experimentation and human models. Such an approach is imperative to reach a mechanism-based diagnostic classification of the RSD/CRPS patients and ultimately to the development of a mechanism-based therapeutic strategy.

**New Research Directions**

The workshop participants identified several critical needs in our basic understanding of RSD/CRPS, as well as potential directions for basic and clinical research on new treatment strategies. These needs were in the areas of: 1) diagnostic criteria, 2) epidemiology, 3) RSD/CRPS model systems, 4) disease mechanisms, 5) integration between basic research and clinical research, and 6) therapy, all of which are explored below.

1) A consensus definition of RSD/CRPS with standardized diagnostic criteria. There is practical agreement among neurologists, anesthesiologists, and others about the minimal clinical criteria (signs and symptoms) that define RSD/CRPS. However, without a universally accepted definition and diagnostic criteria and a further validation and extension of the present clinical criteria, it is difficult to accurately identify RSD/CRPS patients, select patients for clinical trials, validate experimental human and animal model systems for research, and last but not least, to formulate testable hypotheses. The participants suggested that an expert meeting to specifically define the clinical and diagnostic criteria, based on what is known, should be a high priority for the field. Once determined, these consensus criteria should be disseminated to the medical, research, and advocacy communities, in particular to those groups involved in epidemiological studies, design of appropriate models for symptoms in RSD/CRPS, research on underlying mechanisms, and the design RSD/CRPS therapies tested in prospective clinical trials.

2) Epidemiological studies of RSD/CRPS using well defined diagnostic criteria. Epidemiological studies to identify characteristics of patients at high risk for developing RSD/CRPS, to better define the relationship between certain clinical signs and disease onset, progression and distribution on the body, and to determine the incidence of patients with RSD/CRPS were considered a high priority. Patients with RSD/CRPS exhibit different combinations of symptoms. Although the typical patient with RSD/CRPS resolves with appropriate management, there are individual RSD/CRPS patients who progress through the three stages of the disorder as described by some authors. Currently, the symptomatic variability among RSD/CRPS patients makes it difficult to form firm conclusions about mechanisms of the disorder based on clinical profiles, and could contribute to unclear findings in clinical trials. Strict patient selection based on defined clinical criteria could help to resolve this problem. Epidemiological studies may also help to clarify the anecdotal evidence regarding different incidence rates between women and men and the differences in the disease state between.
children and adults with RSD/CRPS. Finally, epidemiological studies may serve to work out prospective studies in order to find predictors for the development of RSD/CRPS.

3) Validate the existing models of CRPS and generate new models that recapitulate the unique features of RSD/CRPS. Appropriate experimental systems in which to study RSD/CRPS are required to advance the field; current model systems do not accurately reflect all of the symptoms experienced by patients, such as the potential gender disparity. We have models to study mechanisms operating in CRPS II (which may develop after trauma with nerve lesion); however, as noted by Dr. Gary Bennett, we almost totally lack animal models to study mechanisms operating in RSD/CRPS (23,39,40). Furthermore, there are few simple in vivo or in vitro experimental model systems available to study potential RSD/CRPS disease mechanisms or to predict the efficacy of potential therapeutics.

4) Define disease mechanisms that give rise to RSD/CRPS in susceptible individuals. Several theories about disease mechanisms were presented at the workshop, but most questions addressing mechanisms clearly remain open. The participants believed that further research efforts focused on determining underlying mechanisms that cause RSD/CRPS are absolutely necessary to make progress in the design of a more appropriate (mechanism-based) diagnostic classification of RSD/CRPS patients and in the design of better therapeutic strategies. In the past, research efforts relevant to RSD/CRPS have generally focused on one component of the syndrome, such as pain, or blood flow, or bone/joint changes, but very little or not at all on CNS components related to the sensory, motor, and sympathetic systems. Because RSD/CRPS affects multiple body systems, it is important to investigate the interactions between these peripheral and central components.

5) Integrate research on animal and human models with clinical research on patients. The workshop participants found it essential (and attractive) that research on (behavioral and reduced) animal and human models and clinical investigations of RSD/CRPS should be closely aligned. Thus, research on mechanisms performed on different models must be interactive with clinical research. Any model, even the human one, is only an approximation to the clinical situation. Research on mechanisms in the models should concentrate on symptoms but not on syndromes.

6) New RSD/CRPS therapies tested in prospective clinical trials. To date, there are no clinical trials on the efficacy of various treatments of RSD/CRPS available that used evidence-based medicine criteria (Dr. David Borsook). The participants presented preliminary anecdotal evidence for therapeutic approaches, such as long-term sympathetic and/or spinal cord blockade and physical therapy that could be tested in controlled, prospective clinical trials. Trials designed to treat patients at risk for developing RSD/CRPS (e.g., those undergoing knee-replacement surgery) would help to standardize the patient populations and may contribute to more reliable clinical results. As suggested by Dr. Howard Fields, a collaborative, multidisciplinary, multicenter translational research program on RSD/CRPS may help to facilitate the development and testing of new therapies for this disorder (16).

In summary, there was a consensus among the participants of the workshop that future research on the mechanisms of RSD/CRPS must be much better integrated with observation on human patients, i.e., with the clinic. Design of behavioral and reduced animal models, including the human models, must be more closely integrated with each other and with the clinic to focus the scientific questions, the formulation of hypotheses, and the experimental approaches. Only such an interdisciplinary and multidisciplinary approach has a realistic chance of uncovering the pathophysiology and improving treatment of RSD/CRPS. Such an approach should be optimal to use and focus the different methodological techniques that are available to reach these aims. The best way to achieve this overall aim is to create research programs in centers in association with the clinic in which RSD/CRPS patients are diagnosed and treated.

References


