Transfer of Complex Regional Pain Syndrome to mice via human autoantibodies is mediated by interleukin-1-induced mechanisms

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Abstract

Neuro-immune interactions may contribute to severe pain, and regional inflammatory and autonomic signs in Complex Regional Pain Syndrome (CRPS), a post-traumatic pain disorder. Here we investigated peripheral and central immune mechanisms in a translational passive transfer-trauma mouse model of CRPS. Small plantar skin-muscle incision was performed in female C57Bl/6 mice treated daily with purified serum-IgG from patients with longstanding CRPS, or healthy volunteers, followed by assessment of paw edema, hyperalgesia, inflammation, and central glial activation. CRPS IgG significantly increased and prolonged swelling and induced stable hyperalgesia of the incised paw compared to IgG from healthy controls. Following a short-lasting paw inflammatory response in all groups, CRPS IgG-injected mice displayed sustained, profound microglia and astrocyte activation in the dorsal horn of the spinal cord and in pain-related brain regions, indicating central sensitization. Genetic deletion of interleukin-1 (IL-1) using IL-1αβ knockout (KO) mice, and perioperative IL-1 receptor type 1 (IL-1R1) blockade with the drug anakinra, but not treatment with the glucocorticoid prednisolone, prevented these changes. Anakinra treatment also reversed the established sensitization phenotype when initiated 8 days after incision. Furthermore, with the generation of a novel IL-1β floxed(fl/fl) mouse line, we demonstrated that CRPS IgG-induced changes are in part mediated by microglia-derived IL-1β, suggesting that both peripheral and central inflammatory mechanisms contribute to the transferred disease phenotype. These results indicate that persistent CRPS is often contributed to by autoantibodies and highlight a potential novel therapeutic use for clinically licensed antagonists, such as anakinra, to prevent or treat CRPS via blocking IL-1 actions.

Significance Statement: Complex Regional Pain Syndrome (CRPS) is a poorly understood painful condition which typically arises after distal limb trauma; 20% of patients may develop lifelong severe incessant pain with few therapeutic options. In this study we show that IgG autoantibodies from patients with severe, persistent CRPS, upon transfer to hindpaw-injured mice elicit important features of the clinical condition, and profound glial activation in pain-related brain regions. Blockade of the proinflammatory cytokine, interleukin-1 (IL-1) both prevents and reverses these changes. Our findings suggest that antibody-mediated autoimmunity contributes to the development of severe CRPS after injury and that blockade of IL-1 actions may be an attractive therapeutic prospect. Investigation of autoantibody contribution to other unexplained chronic pain syndromes appears warranted.


**INTRODUCTION**

Complex Regional Pain Syndrome (CRPS), with a prevalence of about 1:2000, is a chronic pain condition experienced by humans. CRPS is usually triggered by trauma to the distal regions of a limb, and is further associated with limb-restricted edema, sensory, vasomotor, sudomotor, motor, and trophic abnormalities, and profound sensory central nervous system (CNS) reorganisation (1). In CRPS, typically no or only minimal tissue destruction occurs (2), and although morphological change such as disuse atrophy can sometimes be observed, this is not thought to explain the experienced intense pain (3). The underlying pathophysiological mechanisms are poorly understood. Systemic inflammatory markers remain normal in CRPS patients, but regional inflammatory mediators and autoimmunity are suggested to contribute to the manifestation of the symptoms (4). Furthermore, neuro-plasticity mechanisms within the spinal cord and the brain are believed to sustain persistent pain (5).

While most patients with CRPS show an improvement within months, either with or without treatment (6), 20% of patients develop persistent pain, often lasting for years or even through their lifetime (7). This type of persistent pain is intrusive and results in amongst the lowest quality of life scores in medical conditions (8). Among the few drug trials performed to date (9) neither conventional drugs used to relieve pain, (i.e. non-steroidal anti-inflammatory drugs, opioids, anti-depressants, or anti-convulsants), nor steroids have shown significant efficacy in persistent CRPS. Implantation of a spinal cord stimulator, which delivers electrical impulses to the dorsal column can over-ride CRPS pain in about 50% of patients, but the duration of the optimum effect is limited (9). Since many patients cannot be successfully treated, the treatment of CRPS remains an important unresolved problem and is still an unmet medical need (10). Thus, to better understand the peripheral and central pathophysiological mechanisms underlying CRPS, reliable and validated animal models are desperately needed (2).

We have recently shown that passive transfer of serum-IgG from CRPS patients to hindpaw-injured rodents elicits key features (unilateral hyperalgesia and edema) of the clinical condition