

# Autoimmunity in Complex-Regional Pain Syndrome

F. BLAES,<sup>a</sup> M. TSCHERNATSCH,<sup>a</sup> M. E. BRAEU,<sup>b</sup> O. MATZ,<sup>a</sup>  
K. SCHMITZ,<sup>a</sup> D. NASCIMENTO,<sup>a</sup> M. KAPS,<sup>a</sup> AND F. BIRKLEIN<sup>c</sup>

<sup>a</sup>*Department of Neurology, Justus-Liebig-University, Giessen, Germany*

<sup>b</sup>*Department of Anesthesiology, Justus-Liebig-University, Giessen, Germany*

<sup>c</sup>*Department of Neurology, Gutenberg-University, Mainz, Germany*

**ABSTRACT:** Complex regional pain syndrome (CRPS) is an etiologically unclear syndrome with the main symptoms being pain, trophic and autonomic disturbances, and functional impairment that develops after limb trauma or operation and is located at the distal site of the affected limb. Because autoantibodies against nervous system structures have been described in these patients, an autoimmune etiology of CRPS is discussed. These autoantibodies bind to the surface of peripheral autonomic neurons. Using a competitive binding assay, it can be shown that at least some of the CRPS sera bind to the same neuronal epitope. Autoimmune etiology of CRPS is a new pathophysiological concept and may have severe impact on the treatment of this often chronic disease.

**KEYWORDS:** complex regional pain syndrome; autoantibodies; autonomic nervous system

## INTRODUCTION

Complex regional pain syndrome (CRPS, M. Sudeck, sympathetic reflex dystrophy) is a complication that sometimes develops after limb trauma or operation and is mainly characterized by pain, autonomic disturbances, and trophic changes at the distal site of the affected limb.<sup>1</sup> The current diagnostic guidelines distinguish between CRPS without (CRPS type 1) or with obvious nerve lesion (CRPS type 2). The pain is characterized as a severe neuropathic pain, located deep in the limb. Hyperalgesia is present in most patients and additionally, one-third of the patients suffer from allodynia (brush-evoked pain). The autonomic and trophic disturbances include edema and swelling of limb, skin changes, changed growth of hair and nails, and increased or decreased sweating, and can be observed in about 50% of the patients. Motor disturbances are also reported in the majority of CRPS patients. Most of them have a

Address for correspondence: Dr. F. Blaes, Department of Neurology, Justus-Liebig-Universität, Am Steg 14, 35385 Giessen, Germany. Voice: +49-641-9945357; fax: +49-641-9945449.  
franz.blaes@neuro.med.uni-giessen.de

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weakness of the affected limb, but tremor, myoclonus, and focal dystonia can also be observed.<sup>1</sup>

Two main pathogenic mechanisms have been established for CRPS: a neurogenic inflammation at the site of the affected limb and a sympathetic dysfunction both play a role in CRPS. The reason for both mechanisms is still unclear. However, since the first descriptions from W. Mitchell and P. Sudeck,<sup>1</sup> an inflammatory process has been suspected. In the following paragraphs, recent results indicating an involvement of the immune system in the physiopathology of CRPS are reported.

## PHYSIOPATHOLOGY

Two main mechanisms are obviously involved in the physiopathology of CRPS. At the site of the affected limb, an exaggerated inflammation after trauma can be observed. This neurogenic inflammation includes the release of neuropeptides from primary afferent fibers, mainly nociceptive C-fibers. The main neuropeptides released from these fibers are calcitonin-gene-related peptide (CGRP) and substance P (SP). Both peptides can induce local inflammation by increase of plasma extravasation, and activation of other inflammatory cascades.<sup>1</sup>

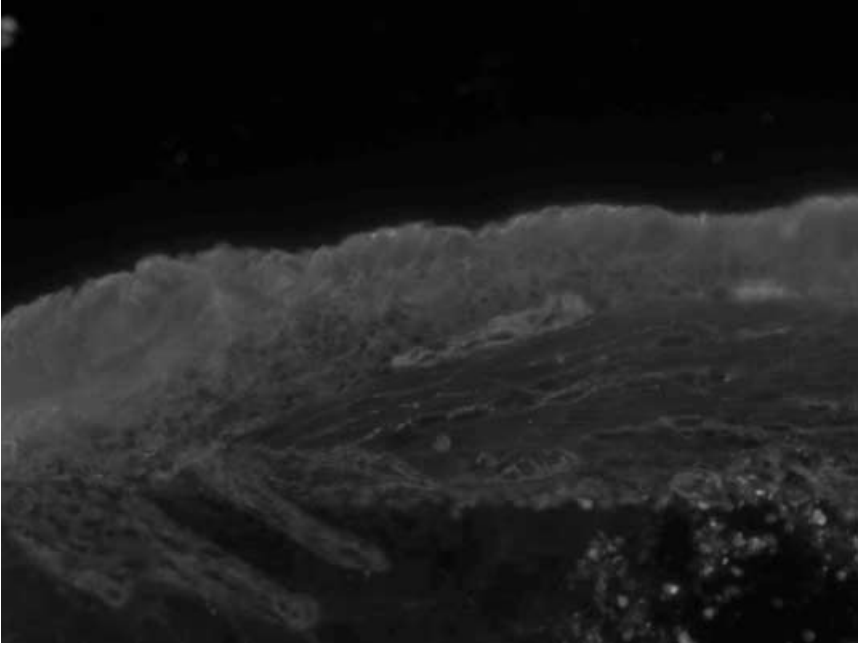
Moreover a sympathetic dysfunction, both locally and within the central nervous system, seems to play a major role in CRPS. Local sympatico-afferent coupling seems to play a role in some CRPS patients, probably induced by the expression of adrenoceptors on primary nociceptive afferents.<sup>2</sup> Patients with CRPS can in parallel show vasoconstrictor hypoactivity and sudomotor hyperactivity. This pattern suggests an involvement of the central thermoregulation system.<sup>3</sup>

## THE ROLE OF THE IMMUNE SYSTEM

Recently, some evidence of an immune system involvement in CRPS has evolved. Some studies revealed an HLA association of CRPS. The alleles DQ1, DR15 are associated with CRPS and in CRPS patients with dystonia DR13 is over-represented.<sup>4,5</sup>

The local cytokine expression at the site of the lesion has been reported in CRPS patients. In the fluid of induced suction blisters of CRPS patients, increased levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6) have been noted.<sup>6</sup> Increased levels of soluble TNF- $\alpha$  receptor type I have been shown to be associated with mechanical hyperalgesia in CRPS.<sup>7</sup>

There is an ongoing discussion about systemic cytokine expression patterns in CRPS patients. Some authors could not detect any abnormalities in IL-1, -6, -8, and -10 blood levels,<sup>8</sup> whereas others could find increased blood levels of



**FIGURE 1.** Immunofluorescence analysis of autoantibodies to autonomic nervous system. Staining of rat gut myenteric plexus by a CRPS serum (arrows). Serum dilution was 1/100, magnification 200 $\times$ .

IL-8 and soluble TNF- $\alpha$  receptor I and II.<sup>9</sup> Moreover, it has been shown that monocytes of CRPS patients have an increased interferon- $\gamma$ -induced NO production, compared to healthy controls.<sup>10</sup> More recently, a significant increase of IL-1 $\beta$  and IL-6, but not TNF- $\alpha$ , has been reported in the cerebrospinal fluid of CRPS patients.<sup>11</sup>

Most treatment approaches in CRPS include symptomatic pain therapy in different forms. However, steroids have shown to be effective in CRPS patients.<sup>12,13</sup> More recently, treatment with intravenous immunoglobulins (IvIg) or anti-TNF antibody has been reported to be effective in single CRPS cases.<sup>14,15</sup>

### AUTOIMMUNE FEATURES

Autoantibodies against autonomic nervous system structures have been described in some patients with CRPS.<sup>16</sup> These autoantibodies were directed against myenteric plexus and sympathetic ganglia (FIG. 1). More recently, another group demonstrate autoantibodies against peripheral nervous system structures in CRPS patients.<sup>17</sup> Using flow cytometry, we could detect

autoantibodies mainly directed against neuronal surface epitopes, which were present in about 60% of CRPS, both type 1 and type 2, but not in healthy controls or trauma patients without CRPS. Interestingly, the surface binding was restricted to differentiated neurons and could not be observed in neuronal (neuroblastoma) or non-neuronal cell lines. In addition, competitive binding assays showed that at least some patients had reactivity against the same antigenic epitope. Autoantibodies directed against surface epitopes have pathogenic effects on their target cells. Autoimmunity against the autonomic nervous system has been reported in different neurological diseases, such as paraneoplastic neurological syndromes, scleroderma, or pure autonomic neuropathies.<sup>18,19</sup> In the latter, surface-binding autoantibodies against neuronal acetylcholine receptors have been proven to be pathogenic.<sup>19</sup> The passive transfer of CRPS IgG into mice in a preliminary study showed disturbed motor functions in the CRPS mice, but not controls.<sup>14</sup> The same group demonstrated a significant clinical improvement of CRPS symptoms after treatment with IvIg, an observation that our own group has also made in some patients recently.<sup>14</sup>

An increased incidence of *Campylobacter jejuni*-IgG in the sera of CRPS patients was recently reported.<sup>17</sup> Recently, we and others could demonstrate an increased prevalence of parvovirus B19-IgG in CRPS patients compared to controls.<sup>20,21</sup> Both infectious agents are known to induce autoimmune diseases. *Campylobacter jejuni* can induce Guillain-Barré syndrome, and parvovirus B19 infections have been linked to autoimmunity in vasculitis syndromes.<sup>22,23</sup> Therefore, these data may point to an infection-triggered autoimmune reaction in some CRPS patients.

## CONCLUSIONS

Increasing data in the recent years link CRPS with disturbances of the immune system. Cytokine patterns are altered locally and systemically and effectiveness of anti-inflammatory or immunomodulatory drugs in CRPS treatment has been shown. The very recent results of two independent groups demonstrating autoantibodies against nervous system structures in CRPS point to an autoimmune etiology of this disease and should stimulate research in this area, including identification of possible autoantigens and functional characterization of the autoantibodies.

## REFERENCES

1. BIRKLEIN, F. 2005. Complex regional pain syndrome. *J. Neurol.* **252**: 131–138.
2. KOLTZENBURG, M. & H.O. HANDWERKER. 1994. Differential ability of human cutaneous nociceptors to signal mechanical pain and to produce vasodilatation. *J. Neurosci.* **14**: 1756–1765.

3. BIRKLEIN, F., B. RIEDL, D. CLAUS, *et al.* 1998. Pattern in autonomic dysfunction in time course of complex regional pain syndrome. *Clin. Auton. Res.* **8**: 79–95.
4. KEMLER, M.A., A.C. VAN DE VUSSE, E.M. VAN DEN BERG-LOONEN, *et al.* 1999. HLA-DQ1 associated with reflex sympathetic dystrophy. *Neurology* **53**: 1350–1351.
5. VAN HILTEN, J.J., W.J. VAN DE BEEK, B.O. ROEP, *et al.* 2000. Multifocal or generalized tonic dystonia of complex regional pain syndrome: a distinct clinical entity associated with HLA-DR13. *Ann. Neurol.* **48**: 113–116.
6. HUYGEN, F.J.P., A.G.J. DE BRUIJN, M.T. DE BRUIN, *et al.* 2002. Evidence for local inflammation in complex regional pain syndrome type 1. *Med. Inflamm.* **11**: 47–51.
7. MAIHOFNER, C., H.O. HANDWERKER, B. NEUNDORFER, *et al.* 2005. Mechanical hyperalgesia in complex regional pain syndrome: a role for TNF-alpha. *Neurology* **65**: 311–313.
8. VAN DE BEEK, W.J.T., E.J. REMARQUE, R.G.J. WESTENDORP, *et al.* 2001. Innate cytokine profile in patients with complex regional pain syndrome is normal. *Pain* **91**: 259–261.
9. SCHINKEL, C., A. GAERTNER, J. ZASPEL, *et al.* 2006. Inflammatory mediators are altered in the acute phase of posttraumatic complex regional pain syndrome. *Clin. J. Pain* **22**: 235–239.
10. HARTRICK, C.T. 2002. Increased production of nitric oxide stimulated by interferon-gamma from peripheral blood monocytes in patients with complex regional pain syndrome. *Neurosci. Lett.* **323**: 75–77.
11. ALEXANDER, G.M., M.A. VAN RIJN, J.J. VAN HILTEN, *et al.* 2005. Changes in the cerebrospinal fluid levels of pro-inflammatory cytokines in CRPS. *Pain* **116**: 213–219.
12. CHRISTENSEN, K., E.M. JENSEN & I. NOER. 1982. The reflex sympathetic dystrophy syndrome response to treatment with systemic corticosteroids. *Acta Chir. Scand.* **148**: 653–655.
13. BRAUS, D.F., J.K. KRAUSS & J. STROBEL. 1994. The shoulder-hand syndrome after stroke: a prospective clinical trial. *Ann. Neurol.* **36**: 728–733.
14. GOEBEL, A., M. STOCK, R. DEACON, *et al.* 2005. Intravenous immunoglobulin response and evidence for pathogenic autoantibodies in a case of complex regional pain syndrome I. *Ann. Neurol.* **57**: 463–464.
15. HUYGEN, F.J., S. NIEHOF, F.J. ZIJLSTRA, *et al.* 2004. Successful treatment of CRPS I with anti-TNF. *J. Pain Symptom Manage.* **27**: 101–103.
16. BLAES, F., K. SCHMITZ, M. TSCHERNATSCH, *et al.* 2004. Autoimmune etiology of complex regional pain syndrome (M. Sudeck). *Neurology* **63**: 1734–1736.
17. GOEBEL, A., H. VOGEL, O. CANERIS, *et al.* 2005. Immune responses to *Campylobacter* and serum autoantibodies in patients with complex regional pain syndrome. *J. Neuroimmunol.* **162**: 184–189.
18. GOLDBLATT, F., T.P. GORDON & S.A. WATERMAN. 2002. Antibody-mediated gastrointestinal dysmotility in scleroderma. *Gastroenterology* **123**: 1144–1150.
19. VERNINO, S., P.A. LOW, R.D. FEALEY, *et al.* 2000. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. *N. Engl. J. Med.* **343**: 847–855.
20. VAN DE VUSSE, A.C., V.J. GOOSSENS, M.A. KEMLER, *et al.* 2001. Screening of patients with complex regional pain syndrome for antecedent infections. *Clin. J. Pain* **17**: 110–114.

21. GROSS, O., M. TSCHERNATSCH, M.E. BRÄU, *et al.* 2007. Increased seroprevalence of parvovirus B19 IgG in complex regional pain syndrome is not associated with antiendothelial autoimmunity. *Eur. J. Pain* **11**: 237–240.
22. WILLISON, H.J. 2005. The immunobiology of Guillain-Barré syndromes. *J. Peripher. Nerv. Syst.* **10**: 94–112.
23. HOLM, J.M., L.K. HANSEN & H. OXHOJ. 1995. Kawasaki disease associated with parvovirus B19 infection. *Eur. J. Pediatr.* **154**: 633–634.