Screening of Patients With Complex Regional Pain Syndrome for Antecedent Infections

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Abstract:

Objective: This study was designed to investigate whether Complex Regional Pain Syndrome type I (CRPS I) could be linked to any previous infection.

Patients: Fifty-two patients with CRPS I of one extremity were screened for the presence of antibodies against mostly neurotropic microorganisms.

Results: Of these 52 patients, none had antibodies against Treponema pallidum, Borrelia burgdorferi, or HTLV-I. Only four patients were positive for Campylobacter jejuni. For cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and Toxoplasma gondii, seroprevalences were similar to control values. The total seroprevalence of Parvovirus B19 in our CRPS population was 77%, which was significantly higher than in an independent Dutch population group (59%). Seroprevalence in lower extremity CRPS I (94%) was significantly higher than in upper extremity CRPS I patients (68%). In this study all patients were seropositive for varicella zoster virus (VZV) antibodies, but a high prevalence of VZV antibodies is similar to its prevalence in a normal population (>90%).

Conclusions: In this study we found a significantly higher seroprevalence of Parvovirus B19 in CRPS I and this is most striking in lower extremity CRPS I patients. Further serologic research in other geographic areas is needed to provide additional information about a potential role of Parvovirus B19 or other microorganisms in the etiopathogenesis of CRPS I.

Key Words: Complex regional pain syndrome—Inflammation—Parvovirus B19—Reflex sympathetic dystrophy—Serologic status—Virus.

Complex regional pain syndrome (CRPS I) is a seriously disabling neuropathic pain syndrome. Its etiopathogenesis remains an enigma. Antecedent infections have been implicated in its pathogenesis, because some of its key features (e.g., edema, pain, vasomotor abnormalities) point to an ongoing inflammatory process. Also, its association with human leucocyte antigen DQ1 suggests an involvement of the immunologic system. In other neurologic disorders of unknown origin progress has been made as to the role of infections as in Bell’s palsy, multiple sclerosis, and Alzheimer dementia. The role of Campylobacter jejuni, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) in the onset of certain forms of Guillain-Barré syndrome is a recent example of research along these lines.

Antecedent infections may have predisposed patients in such a way that a minor trauma resulted in CRPS I. A systematic analysis of the serologic status of CRPS I patients as to antecedent infections has, to our knowledge, not been carried out. We report herein a systemic serologic screening for 10 different microbiological organisms, of 52 strictly diagnosed CRPS I patients.

**PATIENTS AND METHODS**

Sample and data collection

All medical specialists known to treat patients with CRPS I (such as anesthesiologists, surgeons, and
neurologists) working in hospitals in the south of The Netherlands were asked to refer patients fulfilling the standardized diagnostic algorithm (Table 1) to the department of Surgery of the Maastricht University Hospital. The algorithm closely resembles the criteria for complex regional pain syndrome type I (CRPS I), as stated by the International Association for the Study of Pain (IASP). The final decision whether patients could enroll the study was based on rechecking the diagnostic criteria. A physical examination was conducted by two physicians separately, as well as a psychological test (SCL-90). In addition, patients were selected who had suffered from CRPS I for at least 6 months, during which period the symptoms had been unresponsive to all conventional treatments, such as nonsteroidal antiinflammatory drugs, opioids, antidepressants, anticonvulsants, sympathetic blocks, transcutaneous electric nerve stimulation, and physical therapy. Pain, as measured on a 10-cm Visual Analogue Scale, had to be at least 5 cm.

Patients with other conditions affecting function were not included in the study. Informed consent was obtained from all patients according to the Declaration of Helsinki. The study protocol had been approved by the Ethical Committee of our institution.

Eventually, 54 patients were considered eligible for the study and 56 were excluded—40 were not eligible and 16 refused to participate. No blood was drawn from two of the patients included in the study. The reason for this is not known. All 52 remaining patients were white, Dutch-speaking adults (18–65 years of age) suffering from severe CRPS I affecting either one arm (n = 34) or one leg (n = 18).

### TABLE 1. Diagnostic criteria for complex regional pain syndrome type I

<table>
<thead>
<tr>
<th>Absolute criteria</th>
<th>Relative criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Edema</td>
</tr>
<tr>
<td>Impaired function*</td>
<td>Increased nail growth</td>
</tr>
<tr>
<td>Expansion of symptoms outside the area of trauma*</td>
<td>Increased hair growth</td>
</tr>
<tr>
<td>Cold, warm, or intermittent cold-warm feeling in the</td>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td>affected extremity</td>
<td>Abnormal skin coloring</td>
</tr>
<tr>
<td></td>
<td>Hypoesthesia</td>
</tr>
<tr>
<td></td>
<td>Hyperalgesia</td>
</tr>
<tr>
<td></td>
<td>Mechanical and/or thermal allodynia</td>
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<tr>
<td></td>
<td>Patchy demineralization of bone</td>
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</tbody>
</table>

All the absolute criteria, together with at least three of the relative criteria, were needed for the diagnosis of complex regional pain syndrome type I (CRPS I).

*Indicates criteria additional to those of the International Association for the Study of Pain.

Possible involved pathogens were identified by a Medline search from 1966–1997 (key words: serologic, virus, infection, serology, dystrophy, neurotropic and infection or virus), based upon the hypothesis that neurotropic microorganisms could play a role in the etiopathogenesis of CRPS I. Ten ml of serum were frozen and stored at a temperature of −20°C. Serologic status was measured according to standard laboratory procedures of our microbiology department. Detection of IgG antibodies was done with microimmunofluorescence for herpes simplex virus (HSV), varicella zoster virus (VZV) and EBV virus capsid antigen (Gull, ’s Hertogenbosch, The Netherlands). Screening was done with dilution 1:10. Quantification was done with dilutions 1:100, 1:200, 1:400, 1:800, and 1:1600. For anti-Parvovirus B19 IgG antibodies, a qualitative immunofluorescent assay (Biotech, Dublin, Ireland) with dilution 1:64 was done. Campylobacter serology was done with complement fixation and with enzyme-linked immunosorbent assay (ELISA) methodology (Virion, Würzburg, Germany). Anti-CMV and T. gondii IgG antibodies were quantitatively measured by Axsym (Abbott, Hoofddorp, The Netherlands). Treponema pallidum and anti-human T-lymphocyte virus-1 (HTLV-1) antibodies were investigated by agglutination (Fujirebio, Tokyo, Japan) and anti-Borrelia burgdorferi IgG antibodies with ELISA (IDEIA Dako, Cambridgeshire, UK).

Statistical analysis on CRPS I extremity subgroup seroprevalences was performed using either a two-tailed χ² or a Fisher exact test (SPSS 9.0, p <0.05).

**RESULTS**

Fifty-two patients (37 women and 15 men) participated, with a mean age of 38.9 years (range 21–65 years) and a mean CRPS I duration of 37.7 months (9–120 months). Thirty-four had CRPS I of their arm and 18 had CRPS I of their leg. The CRPS I was precipitated by trauma in 25 patients, by surgery in 23 patients, and had started spontaneously in the last four patients. All patients suffered severe pain and functional impairment, which made them unfit for work. Of 34 patients with an affected hand, 20 were unable to use their hand for any daily activity; 13 were using a splint. Of 18 patients with an affected foot, 7 were wheelchair-dependent and 8 were using crutches.

All patients were seropositive for VZV and 50 patients (96%) were seropositive for EBV. For Parvovirus B19 and for HSV the prevalence of antibodies in this group of patients was 77% and 73%, respectively. A lower prevalence was found for CMV (40%), T. gondii (23%) and C. jejuni (8%). All patients were negative for T. pallidum, B. burgdorferi, and HTLV-1 antibodies. Data are given in Tables 2 and 3.
For levels of detectable antibodies, the median immuno- 
fluorescence titer was 100 (range 10–800) for VZV, 
200 (range 10–1600) for HSV and 400 (range 100– 
1600) for EBV. For VZV, HSV, and EBV 21, 18, and 15 pa- 
tients had an above-median titer, respectively. The me- 
dian results for CMV and Toxoplasma were >250 IU/ml 
and 23 IU/ml, respectively. Prevalence of Parvovirus 
B19 infection in lower extremity CRPS is 94% and 
higher than expected. The prevalence is significantly 
more than the 68% seroprevalence of B19 Parvovirus in 
patients with upper extremity CRPS I (p < 0.04). The 
CIJ, Campylobacter jejuni; CMV, cytomegalovirus; HSV, herpes simplex virus; PB19, Parovirus B19; EBV, 
Epstein-Barr virus; VZV, varicella zoster virus.

TABLE 2. Qualitative and quantitative serologic screening in complex regional pain syndrome 
type I

<table>
<thead>
<tr>
<th>Age, y</th>
<th>No. of</th>
<th>Toxoplasma, %</th>
<th>CMV, %</th>
<th>HSV, %</th>
<th>PB19, %</th>
<th>EBV</th>
<th>VZV</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–30</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>4,36</td>
<td>7,64</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>30–40</td>
<td>18</td>
<td>0</td>
<td>2,11</td>
<td>7,39</td>
<td>13,72</td>
<td>14,78</td>
<td>18</td>
</tr>
<tr>
<td>40–50</td>
<td>12</td>
<td>1</td>
<td>5,42</td>
<td>4,33</td>
<td>8,67</td>
<td>10,83</td>
<td>12</td>
</tr>
<tr>
<td>&gt;50</td>
<td>11</td>
<td>2</td>
<td>5,45</td>
<td>6,55</td>
<td>10,91</td>
<td>7,64</td>
<td>11</td>
</tr>
<tr>
<td>Total, %</td>
<td>52</td>
<td>4</td>
<td>12,23</td>
<td>21,40</td>
<td>38,73</td>
<td>40,77</td>
<td>50,96</td>
</tr>
<tr>
<td>Median titer</td>
<td>—</td>
<td>—</td>
<td>23</td>
<td>&gt;250</td>
<td>200</td>
<td>—</td>
<td>400</td>
</tr>
<tr>
<td>Range</td>
<td>—</td>
<td>—</td>
<td>14–88</td>
<td>16–250</td>
<td>10–1600</td>
<td>—</td>
<td>100–1600</td>
</tr>
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</table>

DISCUSSION

Complex regional pain syndrome I is a seriously dis- 
abling neuropathic pain syndrome of unknown patho-
physiology. Although (neurogenic) inflammation has 
been hypothesized to play a role in the pathogenesis of 
the disorder, a systematic search for a microbiological 
infection as a possible causative mechanism has, to our 
knowledge, not been performed. In the past, studies 
along these lines have probably been hampered by lack 
of diagnostic criteria and budgetary restrictions. We re-
port a systematic serologic analysis of 52 carefully diag-
osed CRPS I patients. Our ratio of lower versus upper 
extrremity CRPS I patients (18:34) is comparable to 
the normal ratio of 1:2.19–21 There is an extensive list 
both of possible neurotropic infections in the Western 
world (northwestern Europe) and of pathogens ever 
associated with CRPS I or neurologic diseases. Most 
of these infections are longlasting or latent infections, 
often present since childhood. Also, in our study group 
the duration of the CRPS I had been so long that 
IgM antibodies were not expected anymore. For both 
these reasons, only IgG serology was done. For 
edpidemiologic reasons, we did not screen for pathogens 
such as rabies, JC virus, poliovirus, mumps, and HIV. 
Ethical reasons also kept us from screening for HIV 
infection.

No association was found between CRPS I and 
T. pallidum, B. burgdorferi, or HTLV-1 because all patients 
were seronegative. In contrast, IgG antibodies against 
VZV (100%) and EBV (96%) were present in almost all 
patients. However, this high seroprevalence is not sig-
nificantly different from the high seroprevalence (>90%) 
worldwide or from a seroprevalence of about 75% in 
an independent Dutch control group.16 Because of this 
high seroprevalence, much larger studies or studies in 
other geographic areas would have to be done to prove or 
even exclude an eventual correlation between CRPS I 
and VZV or EBV. The seroprevalence of HSV in the 
CRPS I patients was 73%, which is almost the same as 
the seroprevalence of 68% in the Dutch control group.16

TABLE 3. Percentage of seroprevalence in CRPS I subgroups

<table>
<thead>
<tr>
<th>Type of CRPS</th>
<th>No. of patients</th>
<th>Toxoplasma</th>
<th>CMV</th>
<th>HSV</th>
<th>PB19</th>
<th>EBV</th>
<th>VZV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (%)</td>
<td>37</td>
<td>3</td>
<td>6 (16)</td>
<td>28 (76)</td>
<td>30 (81)</td>
<td>37 (100)</td>
<td>37 (100)</td>
</tr>
<tr>
<td>Men (%)</td>
<td>15</td>
<td>1</td>
<td>6 (40)</td>
<td>10 (67)</td>
<td>10 (67)</td>
<td>13 (87)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Lower extremity CRPS I (%)</td>
<td>18</td>
<td>3 (17)</td>
<td>12 (50)</td>
<td>14 (78)</td>
<td>17 (94)</td>
<td>18 (100)</td>
<td>18 (100)</td>
</tr>
<tr>
<td>Upper extremity CRPS I (%)</td>
<td>34</td>
<td>9 (28)</td>
<td>12 (35)</td>
<td>24 (71)</td>
<td>23 (68)</td>
<td>32 (94)</td>
<td>34 (100)</td>
</tr>
</tbody>
</table>

*Significance: p < 0.05 (two-tailed Fisher exact test).

CRPS I, complex regional pain syndrome I; CMV, cytomegalovirus; HSV, herpes simplex virus; EBV, 
Epstein-Barr virus; VZV, varicella zoster virus.

The prevalences are also comparable with a seroprevalence of 30–50% in higher socioeconomic groups and increased prevalence of 80–100% in lower socioeconomic groups. In female CRPS I patients, the seroprevalence of EBV, HSV, and Parvovirus B19 was 9–14% higher than in male patients. For CMV and for T. gondii the seroprevalence was higher in men. These differences are not statistically significant, possibly because of the low number of patients.

The worldwide seroprevalence of antibodies against CMV ranges from 40 to 100%, depending on the socioeconomic composition of the population. The prevalence of 40% found in our CRPS I patients is lower than a prevalence of 51% found in the Dutch control group. Although in our study only 21 (40%) CRPS I patients were positive for specific anti-CMV antibodies, the titer distribution was skewed by high anti-CMV antibody titers. Thirteen patients had a level of more than 250 IU/ml and six patients had a level between 120 and 250 IU/ml. Only two young women (aged 27 and 29 years) had levels of 16 and 59 IU/ml. The high anti-CMV antibody levels in CRPS I patients probably does not indicate an etiologic role. It is more likely that these high antibody levels are a reflection of a potential reactivation of a latent CMV infection during acute or chronic clinical CRPS I.

The worldwide variation in prevalence of anti-T. gondii antibodies ranges from only 3 to more than 90% of healthy adults, depending of the selected population. Again, the seroprevalence of 23% for anti-T. gondii antibodies in our CRPS I patients is comparable to a prevalence of 22% found in all patients investigated in our hospital in 1997 (unpublished data). Also, the level of antibodies was in accordance with the normal distribution mentioned in unpublished data from Abbott, Hoofddorp, The Netherlands.

Only four patients had detectable antibodies against C. jejuni. However, in two patients this was accompanied by a high titer (128) of complement-binding antibodies, suggesting a recent infection in patients with an already preexisting CRPS I. This means that at the onset of CRPS I probably only two patients were seropositive for anti-C. jejuni antibodies.

The seroprevalence of Parvovirus B19 in our patient population (77%) is higher than the 30–60% mentioned in the literature and significantly higher than the 59% found in a Dutch control group (n = 353). Strikingly, we found in patients with lower extremity involvement (Table 3) that the seroprevalence for Parvovirus B19 is more than 94%. This is significantly higher (p = 0.039) than the 68% seroprevalence of Parvovirus B19 in patients with upper extremity CRPS I. In the lower extremity CRPS I group there is a predominance of women. Women have a slightly higher seroprevalence of anti-Parvovirus B19 antibodies than men. However, this female overrepresentation does not completely explain this difference, because similarly higher seroprevalences for EBV and HSV in women did not result in significant differences between upper and lower extremity subgroups.

The most common manifestation of Parvovirus B19 infection is an erythema infectiosum, also known as fifth disease, with a mild febrile illness and a maculopapular rash ("slapped cheek" appearance) of variable intensity. Besides the erythema, prodromal symptoms and influenza-like illness are also possible, as are arthropathy, transient aplastic crisis, and pregnancy complicated by hydrops fetalis or fetal death. There is evidence that Parvovirus B19 infection induces the production of autoantibodies. It may be associated with rheumatoid arthritis and transient systemic lupus erythematosus-like symptoms. Central nervous system involvement is a rare but well-documented complication of Parvovirus B19 infection in children and adults. Parvovirus B19 has been associated with encephalitis, encephalopathy, aseptic meningitis, ocular neuropathy, and fetal brain infection. In addition, brachial plexus neuropathy, recurrent paresthesias, and numbness and tingling of fingers are associated with Parvovirus B19 infection.

A possible role of Parvovirus B19 in the etiopathogenesis of CRPS I is also suggested by a case report. The prevalence of symptoms in Parvovirus infection is unknown. Parvovirus infection can manifest in subclinical infection or clinical arthralgia. Because many CRPS I patients report diffuse pain without sympathetic dysregulation before CRPS onset, Parvovirus might be a direct precursor of CRPS I. A prospective study for antecedent arthralgias in CRPS I would be interesting. A subclinical Parvovirus infection might well precede CRPS by a period of several months or even years, because auto-immunologic mechanisms through tissue mimicry can manifest slowly.

CONCLUSION

In this study we did not find a clear relation between CRPS I and any of the investigated microorganisms. For Parvovirus B19 we found a significantly higher seroprevalence in patients with CRPS I and this is most striking in lower extremity CRPS I patients. Because of high seroprevalences of VZV, EBV, and HSV in CRPS I patients as well as in a control group, an association between herpesviridae and CRPS I was not found. CMV has probably no etiologic role in CRPS I but reactivation
of a latent CMV infection during CRPS I is possible. Low seroprevalences were found for T. gondii and C. jejuni. No antibodies were found against T. pallidum, B. burgdorferi and HTLV-I. Further serologic research in other geographic areas will have to give additional information about a potential role of Parvovirus B19 or other microorganisms in the etiopathogenesis of CRPS I.

REFERENCES