DOES A VIRAL INFECTION CAUSE COMPLEX REGIONAL PAIN SYNDROME?

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ABSTRACT

(Purpose) Complex regional pain syndrome (CRPS) causes chronic pain and it is an intractable syndrome. The syndrome occurs following blunt trauma, fracture, medical practice (operation, drip infusion, injection, etc.), no inciting event, etc. The affected region is often different from or beyond injured region. Severity of symptoms is completely unrelated to degree of inciting injury. Affected region is inconsistent with a peripheral nerve or spinal root pattern. Symptoms often spread to a variety of directions.

Since 1986, Omura Y. has reported using the Bi-Digital O-Ring Test (BDORT) that was able to determine the kind and amount of concentration of microorganism including virus and bacteria as well as heavy metal, medicine, and so on. According to Omura Y., HSV type I is one of the main causes of intractable pain. We found that Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), and Cytomegalovirus (CMV) were often positive in CRPS patients with indirect BDORT. We hypothesize that HSV, VZV, and CMV are involved in occurrence of CRPS and measured antibody titer of HSV, VZV, and CMV in CRPS patients.

(Materials and Methods) Seventeen CRPS patients were examined for immunoglobulin G (IgG) and IgM antibody titer of HSV and VZV. The patients met Lankford's four cardinal signs and symptoms (pain, swelling, stiffness, and discoloration) for CRPS. The patient group consisted of 16 women and 1 man ranging in age from 14 to 72 years old (mean 46 years old) IgG was measured with solid-phase enzyme immunoassay (EIA) and IgM was measured with captured EIA (SRL, Inc., Tokyo, Japan).

Fourteen CRPS patients were examined for IgG and IgM antibody titer of CMV for the study during the same period. The fourteen patients were included in the 17 patients who had an examination of IgG and IgM antibody titer of HSV and VZV. This patient group consisted of 13 women and 1 man ranging in age from 18 to 72 years old (mean 50 years old). IgG and IgM were measured with a Vitek Immunodiagnostic Assay System (VIDAS) (bioMerieux Japan Ltd., Tokyo, Japan). The VIDAS CMV IgG assay system uses a commercial automated enzyme-linked fluorescent immunoassay (ELFA) for the quantitative measurement of CMV-specific IgG. Readings of more than 6 AU/ml were considered positive according to

manufacturer's recommendations. CMV-specific IgM (CMVM) was similarly measured with the CMVM strips and the CMVM program.

The data in healthy Japanese were obtained from SRL, Inc. (published data and unpublished data). IgG of HSV, VZV, and CMV in the 100 employees were measured with EIA in 1993. The healthy volunteers group consisted of 57 women and 43 men ranging in age from 18 to 54 years old (mean 32 years old).

Positive rate of IgG for the three viruses and average antibody titer of IgG in HSV and VZV were compared between CRPS patient group and the healthy groups. Difference of positive rate of antibody between our study group and the control group was compared using χ^2 test. Difference of average antibody titer between the both groups was compared using unpaired t-test. A P value of less than 0.05 was considered significant in the both comparison.

(Results) CRPS group: HSV IgG was positive in 12 patients (70.6%) and was negative in 5 patients. Average antibody titer was 90.0 ± 23.2 (mean ± standard error). HSV IgM was negative in all 17 patients. VZV IgG was positive in all 17 patients (100%) and its average antibody titer was 26.8 ± 5.2. VZV IgM was negative in all 17 patients. CMV IgG was positive in all 14 patients (100%) and its average antibody titer was 66.6 ± 11.4 UA/ml. CMV IgM was negative in all 14 patients (Fig 3). Control group: HSV IgG was positive in 54 subjects (54%) and negative in 46 subjects. Average antibody titer was 42.3 ± 5.1. VZV IgG was positive in 97 subjects (97%) and negative in 3 subjects. Average antibody titer was 26.2 ± 1.9. CMV IgG was positive in 82 subjects (82%) and negative in 18 subjects. Average antibody titer was 29.4 ± 3.0.

Comparisons in positive rate of antibody (IgG) and average antibody titer (IgG): The differences of positive rate of IgG antibody in three viruses between the both groups were not statistically significant ($P > 0.05$). Although there was no significant difference in titers HSV ($P > 0.05$), the average antibody titers of HSV in CRPS patients were more than twice of those in healthy persons. Titers for VZV were almost equal in the two groups.

(Discussion) Average antibody titers of VZV in CRPS patients group and those in control group were almost equal. However, average antibody titer of HSV in CRPS patients group was more than twice of it in healthy persons group, though there was no significant difference between the both groups. Positive rate of IgG antibody of CRPS group was higher than that of normal group in HSV, though the differences between the two groups were not significant. Takasaki et al. reported that HSV type-1 was inoculated on the shin of the mouse and it caused allodynia and hyperalgesia. The HSV is well known for herpes simplex labialis and herpes simplex genitalis. However, it sometimes causes Bell's palsy through an infection to the facial nerve or encephalitis. Skin eruption is not formed in these diseases. The formation of the herpes depends on infected region. VZV that is in the same family of HSV causes shingles. Shingles is sometimes followed by postherpetic neuralgia (PHN), after the skin eruption is no longer present. PHN resembles CRPS in symptoms. CRPS is mainly found on extremities and skin eruption is not present. If HSV causes CRPS, the comparison is rational. Thus, it is possible that HSV contributes to CRPS.

Many people are infected with HSV and it is latent in nerves. We speculate that decreased immune function may cause reactivation of HSV and then CRPS occurs. Geertzen et al. reported that 80% of all CRPS patients had a recent stressful life-event while only 20% of the control group members reported such an event. We speculate that psychological or social stress lowers local immune function and reactivation of HSV due to lowered local immune function causes CRPS. Circulatory disturbance can also cause reactivation of HSV.

Kemler et al. hypothesized that there was a genetic predisposition to CRPS, and reported that the frequency of human leukocyte antigen (HLA)-DQ1 of CRPS patient significantly increased compared with control frequencies. Those who have an HLA-DQ1 may easily suffer from microorganisms infection. Neumann et al. reported that Borrelia burgdorferi IgG antibody titers were elevated in all four CRPS patients and elevated IgM titer was found in one patient. Although their study did not compare CRPS group with healthy group, structures identical with Borrelia Burgdorferi could be detected on histological sections from the skin of the affected limb in one patient. Gila et al. reported one CRPS patient whose Borrelia Burgdorferi IgG and IgM levels had a progressive increase during three months. Van de Vusse et al. found a significantly higher seroprevelence of Parvovirus B19 in CRPS type1 in a comparison between CRPS patients group and healthy group. The hypothesis that microorganism infection causes CRPS has been advocated for a long time. Among the various proposed theories, the microorganism infection theory is consistent with the following problems in CRPS. Why does CRPS sometimes occur without an inciting event? Why does CRPS sometimes cure without special treatment? Why do only a few persons suffer from CRPS after similar injuries? Why does the patient who did not suffer from CRPS due to previous injuries suffer from CRPS due to another current injury? Why do the signs and symptoms sometimes spread to the other extremities? Hypotheses in CRPS based on mechanism involving abnormalities in pain pathways do not account for the above enigmas.

Measurement of IgG and IgM in paired serum is important in order to confirm virus infection. However, such measurements do not provide sufficient evidence that a virus infection is a cause of CRPS, because it usually takes more than one month from onset of pain until diagnosis. Because patients whose symptoms are intractable inspite of treatment in the other hospitals are often referred to our hospital, the interval between onset of symptom and treatment at our hospital becomes more prolonged. Taking a paired serum samples several months after the onset of pain is not useful. Therefore, we did not take a paired serum samples. We obtain a paired serum samples only if we see a CRPS patient immediately after the onset of pain.

We could not find a study which measured CMV IgG of Japanese healthy persons with ELFA using VIDAS system. One report says that agreement in CMV IgG between the ELFA and ELISA of a company and was more than 99%. Another reports that agreement in CMV IgG between the ELFA and EIA of a company was more than 99%. It is most likely that positive rates of CMV IgG among EIA, ELISA, and ELFA are almost the identical.

This study did not definitively prove that HSV infection is a cause of CRPS. We will conduct a future study.