

IgE-Mediated Hypersensitivity: Patients with Complex Regional Pain Syndrome Type 1 (CRPS1) vs the Dutch Population. A Retrospective Study

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ABSTRACT

Objective. To investigate whether hypersensitivity is more common in Complex Regional Pain Syndrome type 1 (CRPS1) patients than in the general population. In a recent study, the level of tryptase, a specific marker for mast cells, was significantly higher in blister fluid from the involved extremity of CRPS1 patients. This suggested that mast cells may play a role in the pathophysiology of CRPS1. Mast cells are major effectors in allergic reactions, and are also involved in a variety of noninfectious inflammatory diseases.

Patients. Sixty-six Dutch patients with CRPS1 in one extremity were included.

Outcome Measures. Allergy information was obtained from the medical history and a modified questionnaire based on the *Europees Luchtweg Onderzoek Nederland 1* study. Total IgE and allergen-specific IgE were measured from blood samples. Also tryptase, as a marker for mast cells, was measured. The data from the questionnaire were compared with that of the general Dutch population, and the plasma levels were compared with reference values and data in the literature.

Results. The medical history did not differ from information provided in the questionnaire by the CRPS1 group. There was no significant difference between the answers to the questionnaire between the CRPS1 patients and the general population. The total IgE levels were elevated in 30% of the CRPS1 patients compared with 15–24% of the general population, and allergen-specific IgE and tryptase levels were comparable with the reference values.

Conclusions. Based on the medical history, an allergy questionnaire, and objective laboratory findings we conclude that IgE-mediated hypersensitivity is not more common in CRPS1 patients than in the general population.

Key Words. Complex Regional Pain Syndrome; Hypersensitivity; Mast Cells

Introduction

Complex Regional Pain Syndrome type 1 (CRPS1) is a disease in the distal part of an extremity that usually occurs as a complication after surgery or trauma, although spontaneous occurrence has also been described [1].

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The pathophysiology of CRPS1 remains a matter of debate. In general, three mechanisms are thought to be involved: afferent mechanisms (e.g., neurogenic inflammation), efferent mechanisms (e.g., autonomic disturbances), and central nervous system mechanisms (e.g., cerebral plasticity). Based on our review of the literature regarding the CRPS pathophysiology, we hypothesized that after trauma or surgery, the normal sterile inflammatory response is exacerbated by a genetic and/or acquired immunologic disorder [2]. Neuroimmune activation of cells in the peripheral

Table 1 Modified diagnostic criteria for the Complex Regional Pain Syndrome type 1 [18]

Continuing Pain Which Is Disproportionate to Any Inciting Event	Report of at Least One Symptom in Each of the Following Categories	Must Display at Least One Sign in Two or More of the Following Categories
Sensory:	Hyperesthesia	Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch)
Vasomotor:	Temperature asymmetry and/or skin color changes and/or asymmetry	Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
Sudomotor/edema:	Edema and/or sweating changes and/or asymmetry	Evidence of edema and/or sweating changes and/or asymmetry
Motor/trophic:	Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)	Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

nervous system, which is part of the afferent mechanism, apparently results in sensitization of the central nervous system, which is clinically displayed as allodynia and hyperalgesia [3]. Neuropeptides, cytokines, and other mediators are released during this inflammation [4,5] and cause the classical signs and symptoms, which resemble inflammation. These include increased skin temperature, edema, pain (allodynia, hyperalgesia), loss of function, and redness [2,6].

We showed that the levels of the cytokines tumor necrosis factor alpha (TNF- α) and interleukin-6 (IL-6) in fluid from artificially made skin blisters on the involved and contralateral extremities of patients with CRPS1 in one extremity are significantly higher in the involved extremity [4,7]. A wide range of cells, such as activated T lymphocytes, monocytes, macrophages, and skin resident cells such as mast cells, could contribute to the production of these cytokines. The involvement of lymphocytes and macrophages is relatively difficult to determine. But the involvement of mast cells is relatively easy to detect by measuring tryptase, a specific marker for mast cells [8].

Mast cells are major effectors in allergic reactions, and are also involved in a variety of non-infectious inflammatory diseases [9]. They have many important functions, especially for innate and adaptive immunity, inflammation, and tissue remodelling [10]. Mast cells are situated around dermal blood vessels [11] and are in close proximity to nerves in various tissues, including skin, lung and the intestinal mucosa [9,12,13] and a higher number of mast cells have been found in the distal part of extremities [11]. Local activated mast cells release vasoactive mediators (histamine, leukotrienes, and prostaglandin D₂) and other biologically active molecules (interleukins, proteases and heparin) [14] which causes the wheal-and-flare reaction of the skin [15,16].

Our group measured a significantly higher level of tryptase in blister fluid from the involved extremity which suggested that mast cells may play a role in the production of cytokines such as TNF- α and IL-6 in CRPS1 [17]. Because mast cells are also involved in allergic disease, the aim of the study was to investigate whether IgE-mediated hypersensitivity is more common in CRPS1 patients than in a reference population.

Methods

The protocol was approved by the Medical Ethics Committee of the Erasmus MC, Rotterdam (MEC no. 1989.780/2001/24). All patients gave informed consent. The guidelines of the Declaration of Helsinki (amended version of 2002) and Good Clinical Practice (ICH/GCP version 1996) were followed. Data collection and calculations were performed according to guidelines for registration of personal data.

Patients

Sixty-six patients with CRPS1 in one extremity, as defined by the diagnostic criteria of Harden [18] (see Table 1), were included in the study. These patients have participated in several studies performed between 2001 and 2005, either to investigate the pathophysiology of CRPS1 or the effects of specific treatment regimens [4,7,17,19].

Registration of Allergy

We obtained data on allergy through a medical history taken at the screenings visit to our clinic, prior to the start of medication, between 2001 and 2005. In 2006, all patients received a modified questionnaire based on the Europees Luchtweg Onderzoek Nederland (ELON) I study, a Dutch arm of the European Community Respiratory Health Survey I (ECRHS1) [20,21]. Questions

about respiratory symptoms concerning asthma, nasal allergies, hay fever, and skin allergies were adopted from the Dutch version of the ECRHS questionnaire.

Those who participated in the ELON I study are representative of the Dutch population in general, and were used as a control group. This group was divided into two age groups; a group aged 44 years and younger, and a second group aged 45 years and older. The reason for this was that the first part of the ELON I study was conducted in the 44 years and younger age group, and the investigators wanted to also obtain information about those older than 44 years. The CRPS1 population was also split into similar age groups for comparison.

Plasma

EDTA blood samples (7 mL) were collected from the patients during their screenings visit to our clinic, prior to the start of medication, between 2001 and 2005. In 50 patients with CRPS1 in the upper extremity, blood was obtained by venapuncture in the involved extremity and a control sample was taken from the contralateral extremity. In 16 patients with CRPS1 in the lower extremity, blood was drawn from the involved extremity, and a control sample was taken from the upper extremity by venapuncture. The plasma was isolated by centrifugation at 2650 g_{max} for 10 minutes at 20°C. The samples were stored at -80°C until analysis.

Laboratory Assays

Total IgE, specific IgE against a mixture of inhalant allergens (PhadiaTOP), specific IgE against a mixture of food allergens (fx6 food mix), and tryptase were determined with the ImmunoCAP system (Phadia, Nieuwegein, The Netherlands) according to the manufacturers' instructions. The detection limit for total IgE was 2 kU/L; a value of 1 kU/L was given to total serum IgE levels below 2 kU/L. The detection limits for specific IgE and tryptase were 0.35 kU/L it and 1 µg/L, respectively. The Phadia tryptase assay detects both α-tryptase and β-tryptase.

The inhalant allergens mixture (Phadiatop) contained house dust mites, cat, horse, and dog dandruff, grass pollen mixture, mold mixture, tree pollen mixture, herb pollen mixture, and olive tree pollen. The food-allergen mixture consisted of the following allergen groups: chicken egg whites, cow's milk, codfish, wheat, peanut, and soy.

The levels of C-reactive protein (CRP) were measured with a high-sensitivity assay (hs-CRP)

with the Immage 800 Immunochemistry System (Beckman Coulter, Mijdrecht, The Netherlands). The assay is calibrated against the College of American Pathologists standard for hs-CRP, with a range from 0.2–1,440 mg/L. All measurements were performed in the laboratories of the department of clinical chemistry of the Erasmus Medical Center, Rotterdam, The Netherlands.

Statistical Analysis

Data were analyzed with SPSS for Windows, version 14.0. For analysis of the questionnaire, the cross-tabs were calculated and the results were analyzed with the chi-square test. A P value ≤ 0.05 divided by the number of comparisons (13 questions) was considered to indicate a significant difference (a Bonferroni correction). Correlation of paired samples was calculated for laboratory analysis using Spearman's Rank Correlation test. A P value ≤ 0.05 was considered to indicate a significant correlation.

Results

A group of 66 patients with CRPS1 in one extremity, with no systemic inflammation involved (normal levels of CRP in plasma), was included in this study. The characteristics of the patients are presented in Table 2.

Thirty-three of the 62 patients reported an allergy in their medical history. No information about allergies was available for four patients. An allergy to antibiotics was reported by 24.2%, to NSAIDs by 9%, and for corticosteroids and calcium antagonists by 3% each. A skin reaction, mainly caused by plasters and metals, was reported by 39.4% of these patients and 6% reported an allergy to insect bites. An allergy caused mainly by pollen and house dust mites was reported by 24.2% of the patients, and a food allergy was reported by 6%.

Table 2 Characteristics of the study population

Patient Characteristic	Value
Gender: male/female	16/50
Age in years	50 (21–80)
Duration of CRPS1, months	22 (2–193)
Location: upper/lower extremity	50/16
Side: right/left	34/32
Cause: trauma (fracture, accident)/surgery/spontaneous/other	40 (25, 15)/17/2/7
Plasma C-reactive protein: involved side/contralateral side (mg/L)	2.8 (0.2–39.4)/2.6 (0.2–43.7)

Data are presented as median (range).
CRPS1 = Complex Regional Pain Syndrome type 1.

Table 3 Allergy questionnaire: CRPS1 patients and the Dutch population

	CRPS1 Patients (N = 20) ≤44 years (% yes)	Dutch Population (N = 1,314) ≤44 years (% yes)	P Value	CRPS1 Patients (N = 35) ≥45 years (% yes)	Dutch Population (N = 1,397) ≥45 years (% yes)	P Value
Nasal allergy including hay fever?	35.0	18.7	0.081	23.5	14.1	0.134
Wheezing or whistling in your chest?	10.0	20.4	0.399	25.7	26.9	1.000
If yes, were you short of breath?	30.0	14.3	0.058	22.9	17.1	0.366
If yes, you did not have a cold?	15.0	12.2	0.727	23.5	13.8	0.129
Woken up with a feeling of tightness in your chest?	5.0	8.8	1.000	15.6	15.3	0.367
Woken up by an attack of shortness of breath?	15.0	4.9	0.075	6.3	7.8	1.000
Woken up by an attack of coughing?	40.0	30.3	0.338	15.6	33.4	0.036
Medication taken for asthma?	10.0	2.1	0.072	8.6	2.9	0.089
Trees, grass, flowers or a lot of pollen in the air:						
Get runny or stuffy nose?	35.0	18.1	0.074	26.5	14.7	0.083
Get itchy or watering eyes?	35.0	14.4	0.019	17.6	10.5	0.168
Feathers or dust:						
Get runny or stuffy nose?	42.1	27.2	0.192	20.0	16.4	0.497
Get itchy or watering eyes?	15.0	14.7	1.000	8.6	9.8	1.000
Eczema or any kind of skin allergy?	57.9	36.2	0.058	28.6	29.9	1.000

Chi-square test *P* value < 0.05/13 (Bonferroni correction).

CRPS1 = Complex Regional Pain Syndrome type 1.

The modified questionnaire was sent to the 66 CRPS1 patients, but 11 were not returned. No difference was found in the CRPS1 group between the answers given on the medical history and the answers given on the questionnaire. Based on the chi-square test, no significant difference in answers between the CRPS1 population and the controls in both age groups was found (Table 3).

Plasma was available from 63 of the 66 CRPS1 patients. A normal level of total serum IgE (<100 kU/L) was found in the plasma of 70% of the 63 CRPS1 patients (range; 2–83 kU/L). There was an increase in the IgE level (>100 kU/L) in the other 30% of the patients (range; 109–1,900 kU/L). The measurements for allergen-specific IgE were performed for aeroallergens and for food allergens. In 62 patients (94%), no IgE against food allergens was found (<0.35 kU/L). In 68% of the patients, no IgE against inhalant allergens was found (<0.35 kU/L). In the other 32% of patients, the levels of aeroallergen-specific IgE were elevated compared with the reference value of <0.35 kU/L, with a range of 0.36–27.6 kU/L. The levels of tryptase were normal (<11.4 µg/L) in 91% of the patients (range; 2.0–10.2 µg/L), but were elevated in 9% of the patients (range; 11.5–19.6 µg/L).

Discussion

In this study, similar answers were given on the medical history and on the questionnaire based on the ELON I study in the CRPS1 population. We

also did not find any significant difference between the CRPS1 population and the general population. In the plasma of the CRPS1 patients, only a slight increase in tryptase was found. Total IgE was increased in 30% of the patients, but the levels of aeroallergen-specific IgE and food allergen-specific IgE were normal compared with the reference values.

Allergic asthma, allergic rhinitis (hay fever), or atopic eczema are frequent conditions and affect at least 20% and up to 40% of the adult individuals in Western societies [22–24]. Allergic rhinitis is the most frequent condition. In recent decades, it is suggested that the prevalence of these conditions has increased [23,25]. The ELON I study was performed in 1992, and our patients filled out the questionnaire in 2006. If the suggestion of increased atopy during the last decade were true, repetition of the ELON I study would give a higher prevalence of symptoms at the present time. One possibility would be that the percentages from the CRPS1 population would be even lower than in the general Dutch population instead of the same.

In the pathogenesis of allergic reaction, mast cells are involved in some inflammatory skin reactions [16] and in inflammatory reactions in CRPS1 patients [17]. When mast cells are activated by specific antigens, surface-bound antigen-specific IgE [22,26,27] or stress local degranulation of the secretory granules may occur [28]. This can cause release of vasoactive mediators and other biologically active molecules [14] and may induce the

wheel-and-flare reaction of the skin [15,16]. This local reaction may play a role in CRPS1 and may cause the redness and swelling in the acute stage of the disease. In the plasma of CRPS1 patients, an increase in IL-8 was found by Schinkel et al., but no increase in IL-6 was found [29]. Van de Beek et al. could not find any increase in cytokines in the plasma of CRPS1 patients [30]. However, in the blister fluid of patients with CRPS1, the interleukins TNF- α and IL-6 are increased in the involved extremity [4,31]. This may indicate a local process with no systemic activation of these cells.

Tryptase is a good marker for systemic mast cell activation [10,27,32]. Min et al. found that the levels of total tryptase are higher in men than in women [33]. But there are several diseases, for example Multiple Sclerosis, which occur more often in women than in men and the levels of tryptase and histamine are found to be higher in the cerebral spinal fluid. CRPS1 also occurs more often in women than in men [34]. Huygen et al. found significantly higher levels of tryptase in suction blister fluid from the involved extremity of CRPS1 patients [17], but we could not find significantly increased levels of tryptase in the plasma from our patients. This may indicate a local role for mast cells in CRPS1 rather than a systemic one.

IgE-mediated hypersensitivity consists of two stages. The initial sensitization phase occurs following exposure of a predisposed but IgE antibody-negative individual to an allergenic substance; for example, house dust mites. This will lead to production of specific IgE antibodies. IgE circulates in the blood and binds to high affinity epsilon Fc-receptors on mast cells and basophils. In the second phase, the sensitized individual may experience any of a spectrum of allergy symptoms upon re-exposure to the same allergen. These symptoms can range from asthma, urticaria, or anaphylactic shock. Only 50% of those sensitized to allergens express these symptoms [35]. IgE can be increased in all kinds of diseases, such as in atopy, infection, immunological disorders, or parasitic disease, and also in people without disease. This means that total IgE has a very limited diagnostic value for any condition. It is only a good indicator of the prevalence of sensitization to allergens in the population and to decide if further research is necessary [22,27,36,37]. Because of the presence of increased total IgE in many diseases, we measured IgE in the plasma of CRPS1 patients. We found an elevated level of

IgE in 30% of the CRPS1 patients, which is higher than the 15–24% reported in the literature [38–40]. A possible sensitization to allergens might be on hand, and to confirm or exclude this it is necessary to perform specific IgE tests to common aeroallergens and food allergens.

Hypersensitivity to aeroallergens and food hypersensitivity are both based on a IgE-dependent mechanism, and mast cells and cytokines are the things involved in this mechanism [15] as well as in CRPS1 [4,17]. The next research step for us in CRPS was to investigate whether patients with CRPS1 are hypersensitive to aeroallergens and food allergens. It is important to first look at the clinical history of the patient to diagnose hypersensitivity to aeroallergens and food allergens. The diagnosis can be further established with either skin-prick tests or measurement of specific IgE [23,27]. The skin-prick test was not possible in the CRPS1 population because we were no longer seeing the patients in our clinic. We were only able to measure the aeroallergen-specific and food allergen-specific IgE in the plasma we had in stock from this population.

At least one positive specific IgE test to common inhalant aeroallergens is seen as the golden standard for sensitization [36]. In 32% of the general Dutch population, Kerkhof et al. found at least one positive allergen-specific IgE test in both men and women [41]. This is exactly the same percentage we found in our CRPS1 population. This means that the level of allergen-specific IgE in CRPS1 patients does not deviate from the general Dutch population. Therefore, we conclude that CRPS1 patients do not have a higher prevalence of hypersensitivity to aeroallergens.

The prevalence of food hypersensitivity in adults is about 3%, and has increased in recent decades in the general adult population. But there is a large discrepancy between the self-reported prevalence and the confirmed prevalence by food challenge (10–14% vs 3–3.2%) [15,42,43]. In our population 6% reported a food allergy during the medical history, but a slight increase in food specific IgE was found in only one patient (1.6% of the total group). These percentages are lower than those in the general population, which means that our population does not have hypersensitivity to food.

In summary, based on the medical history, an allergy questionnaire, and objective laboratory findings we conclude that IgE-mediated hypersensitivity for aeroallergens and for food allergens is not more common in CRPS1 patients than in the general Dutch population.

Acknowledgment

This study was performed within Trauma-Related Neuronal Dysfunction, a knowledge consortium that integrates research on CRPS1. The project was supported by a Dutch Government Grant (BSIK03016). The laboratory analysis performed by Mr. Kurstjens was highly appreciated, and the authors also thank Dr. Dirk Stronks (Pain Knowledge Centre) for the statistical analysis.

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