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Review

Complex regional pain syndrome, prototype of a novel kind of autoimmune disease ☆

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ABSTRACT

Complex regional pain syndrome (CRPS) is a painful condition, which arises in a limb after trauma. CRPS can profoundly affect patients' quality of life, and there is no cure. CRPS is associated with limb-confined sensory, motor, skin, bone and autonomic abnormalities. Recent research has shown that some patients respond to treatment with immunoglobulins, and that a majority have IgG serum-autoantibodies directed against, and activating autonomic receptors. CRPS serum-IgG, when transferred to mice elicits abnormal behaviour. These results suggest that CRPS is associated with an autoantibody-mediated autoimmune process in some cases. CRPS has unusual features, including a non-destructive, and regionally-confined course. We propose that CRPS constitutes a prototype of a new kind of autoimmunity, which we term 'IRAM' (injury-triggered, regionally-restricted autoantibody-mediated autoimmune disorder with minimally-destructive course). Understanding autoimmune contribution to CRPS should allow the exploration of novel treatment modalities in the future. Additional 'functional' disorders, painful or painless may be autoimmune in nature.

Contents

1. Introduction

Around the time when Paul Ehrlich described 'horror autotoxicus', the postulate that our body does *not* tolerate an immune reaction against itself, Paul Sudeck reported on a peculiar painful post-traumatic condition [1,2] (Weir Mitchell had first described in 1864, what was later recognized as a post-nerve injury form of the same condition; this rare subgroup is now classified as 'CRPS II'; Mitchell had termed the syndrome he had observed 'causalgia' after the reported peculiar, burning pain). In 1900, Sudeck portrayed five patients admitted to the General Hospital in Hamburg, Germany, who had sustained peripheral limb trauma and developed disproportionate, un-abiding limb pain, associated with limb-confined swelling, sweating and reddening. He initially considered that these signs and symptoms were caused by a particular inflammatory reaction. He identified localized osteoporosis on X-ray and thus assigned the term 'acute, entzuendliche Knochenatrophy' (acute inflammatory bone atrophy). This syndrome subsequently received a number of additional names including 'Sudeck's atrophy' and 'Reflex Sympathetic Dystrophy', until in 1994 'complex regional pain syndrome' (CRPS) was accepted [3]. The diagnostic 'Budapest' criteria are based on the presence of pain and certain limb abnormalities including sensory, autonomic, trophic and motor changes [4]. CRPS is costly to both the healthcare system and society. Only few patients with un-abiding CRPS to work [5]. There are only few treatments, and there is no cure [6,7]. The condition has continued to puzzle investigators. Bizarre aspects of its presentation have continued to emerge over the past 110 years, and although we now understand that CRPS is indeed associated with an initial local inflammatory response – without reported neutrophil invasion or overt

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tissue destruction [8] – the underlying cause has remained elusive. Over the course of the disease, initial limb signs generally mellow [9], however about 15% of patients continue to have unrelenting pain [5]; these patients' quality of life remains amongst the lowest reported in medical conditions [6].

We propose that in some cases CRPS is autoimmune-mediated, caused by a novel kind of autoimmunity, which has unusual features. One important feature is, that CRPS is post-traumatic, and that certain parts of the body – the peripheral limbs – are susceptible [10]. Stable regional restriction of autoimmunity within a larger organ is rare; it occurs, for example in ophiasis, an occipital form of alopecia areata, which is T-cell mediated [11]. A 'two-hit' process may explain a regional restriction. Pre-existing circulating autoantibodies (the 'first hit') may become pathogenic only in the context, and around the area of regional trauma (the second hit, Fig. 1A). Peripheral limbs may provide a facilitating environment. One additional unusual CRPS feature is minimal tissue destruction, even after many years disease duration. Other CRPS characteristics accord with a 'classical' autoimmune presentation. CRPS is usually of adult onset [12]. There are HLA associations, although most studies have been small [13]. A number of investigators have described cases following viral and bacterial infections [14,15]; further we have provided preliminary serological evidence for antecedent infections with chlamydia, parvovirus and campylobacter [16–18].

Based on recent laboratory and clinical findings described below we suggest that autoimmune-associated CRPS should be classified an injury-triggered, regionally-restricted autoantibody-mediated autoimmune disorder with minimally-destructive course (IRAM). The focus of this paper is to describe the evidence, which has led us to propose an autoimmune aetiology for CRPS, and discuss conceptual challenges.

2. Clinical and laboratory findings

Our groups have begun to research the possible autoimmune aetiology of CRPS after independent, serendipitous observations.

In the late 1980s Prof. Guenter Sprotte and Dr. Robert Schedel at the University Pain Clinic in Wuerzburg, Germany observed that a patient with unexplained chronic pain (not CRPS) experienced reproducible, dramatic pain relief each time when she received low-dose intravenous immunoglobulin (IVIG) treatment for her concomitant hypogammaglobulinaemia (Prof. Sprotte, personal communication).

- In a subsequent open investigation in 130 patients with chronic pain, without obvious concomitant immune disorders, we found very good

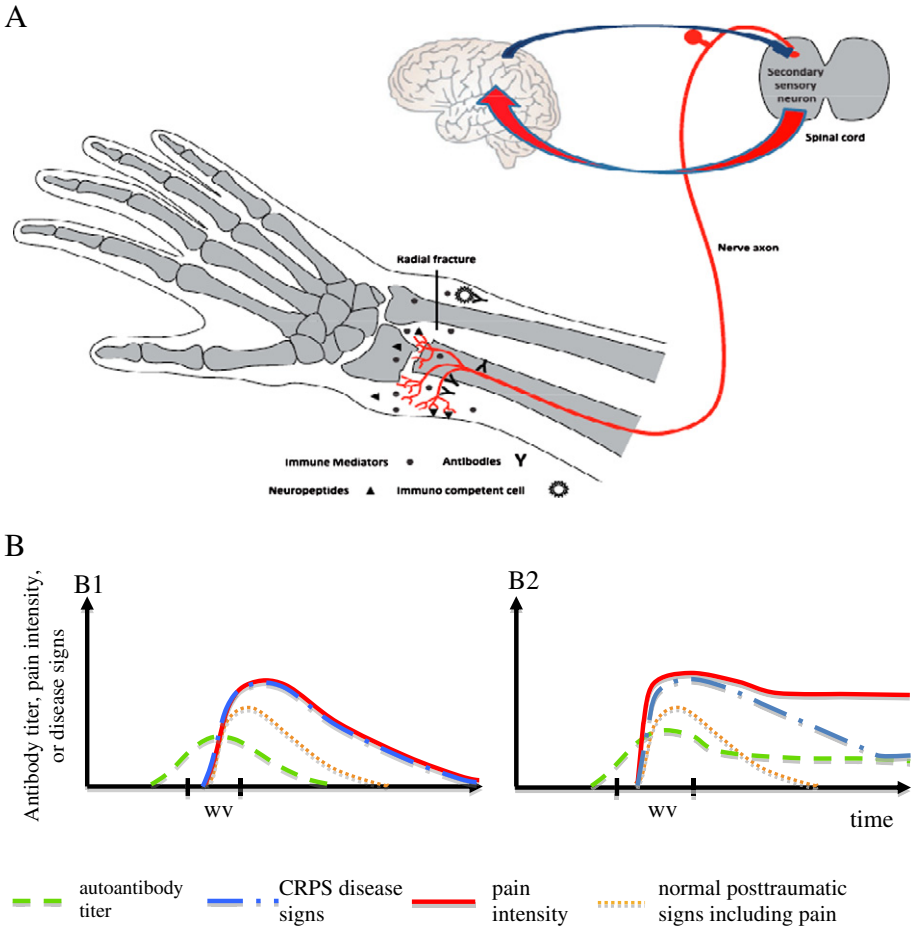

Fig. 1. *A. Conceptual model of autoantibody-mediated CRPS.* The tissues affected by limb injury release inflammatory mediators, including neuropeptides; this environment facilitates the binding of circulating pathogenic IgG autoantibodies. Autoantibodies sensitise primary sensory neurons, either directly, or indirectly (through triggering the release of additional mediators); this process, in turn causes central sensitization (see text) in the spinal cord dorsal horn, perpetuating the perception of pain. Antidromic neuropeptide release from sensory nerves may be partially under cortical control. B. *Simplified hypothetical relationship between autoantibody titre, CRPS disease signs, and pain intensity.* B1 quickly resolving CRPS: if limb trauma occurs (window of vulnerability, wv) of a high titre of relevant autoantibodies (green dashed line), then a post traumatic reaction ensues, with disease signs such as enhanced swelling, and temperature changes, blue line dash-dot, and high pain intensity (red line), fulfilling diagnostic criteria for CRPS; however as the AAB titre naturally normalizes, so do these CRPS features; B2 un-resolving CRPS: here the autoantibody titre only partially normalises, and whilst the initial post-traumatic reaction may slowly reduce through natural anti-inflammatory mechanisms, binding autoantibodies continue to sustain central sensitisation. Orange dotted line: normal course of swelling and pain after radius fracture.
Panel A is adapted from Goebel A. Rheumatology 2011, with permission.

(>70%) pain relief to low-dose IVIG treatment in subgroups of patients with various types of unexplained chronic pains, including three of eleven patients with CRPS (27%). Response to IVIG is considered circumstantial evidence for an autoimmune aetiology [19].

- We consequently considered the possibility that an infection-triggered autoimmune process might produce cross-reactive autoantibodies, and began to investigate patients' sera for evidence for post-infectious immune responses. We found that patients' sera contain IgM and IgG antibodies against certain bacterial and viral surface epitopes with significant higher frequency, than sera from healthy control subjects [16–18].
- In order to explore a pathophysiological contribution of IgG serum-autoantibodies, we injected serum-IgG from one patient with longstanding CRPS into groups of mice ('passive transfer'), and found marked depression of 'rearing', an exploratory behaviour, when compared to healthy-control serum-IgG injected groups. These results strengthen the possibility of a serum-autoantibody contribution to causing CRPS [20]; we did not test for specific CRPS signs.
- To both confirm the pain-relieving effect of low-dose IVIG in-, and detail any autoantibody contribution to CRPS, we conducted a randomized controlled crossover trial of immunoglobulin treatment and took sera from the trial participants before treatment. The trial results confirmed that some patients with longstanding (6 months to 2.5 years) CRPS will experience both dramatic pain reduction, and improvements in their limb signs after a single low-dose (0.5 g/kg) IVIG infusion, with effects lasting no more than 3 months [21]. In IgG-transfer experiments, the IgG fractions from RCT participants again caused rearing depression in mice. However the animals did not develop CRPS-typical signs, such as obvious swelling, or sensitivity to heat, cold or punctuate stimulation, suggesting the value of extending the passive-transfer model with the application of limb trauma [22].

We made an independent serendipitous observation in 2002, when the serum of a patient for whom immune autonomic neuropathy had first been suspected was sent to our autoimmune laboratory. This patient in fact had CRPS, and his serum contained autoantibodies against autonomic nervous system structures (myenteric plexus and sympathetic neurons).

- In subsequent investigations we found that CRPS sera often stain rodent sympathetic ganglia (myenteric plexus and superior cervical ganglion cells, 5/12 CRPS-, 1/20 non-inflammatory peripheral neuropathy-, and 0/20 healthy control preparations were positive) [23], thus providing support for the presence of anti-sympathetic autoantibodies.
- In parallel experiments, we stained rodent peripheral nerves and found that CRPS sera bound stronger than sera from healthy volunteers [16].
- Using Fluorescence Activated Cell Sorting (FACS), we confirmed that CRPS serum-IgG preparations bind to primary sympathetic cells more often than controls (binding of CRPS serum-IgG, or serum-IgG from patients with non-inflammatory neuropathies, posttraumatic neuropathies, or healthy volunteers was observed in 43%, 5%, 5%, 0% of cases respectively). Patients with, or without such anti-autonomic autoantibodies did not differ in their demographical or clinical features [24].
- To explore the presence of functionally active autoantibodies directed against receptors of the autonomic nervous system, we next used a cardiomyocyte model, where activation of both muscarinergic and adrenergic receptors is reflected in changes in the beating frequency of spontaneously beating foetal cells. We found that IgG preparations from patients with early CRPS, but not from healthy controls, or control-patients with posttraumatic neuropathies, induced changes to these cells' beating frequencies. These changes were abrogated by pre-incubation with a combination of atropine and propanolol, suggesting a combined IgG effect against two autonomic receptors. We further found that the serum-IgG from 90% of patients bound to specific peptide sequences from the second extracellular loop of the M-2 muscarinergic and/or the beta-2 adrenergic receptors [25].
- Finally we investigated functional effects of CRPS serum-IgG taken from twelve IVIG-RCT participants (see above), using an adult primary rat cardiomyocyte model and were able to confirm the anti-muscarinerinic effect. In addition we found evidence for an additional type of anti-autonomic activity, and initial evidence that certain autoantibody profiles may predict the clinical response to IVIG (unpublished data).

In summary, the responsiveness of some patients to treatment with intravenous immunoglobulin provided a first, circumstantial evidence for a role for autoimmune factors. Immunohistochemical, behavioural, ex-vivo and in-vitro experiments then indicated a possible directly pathogenic role for IgG serum-autoantibodies, and identified surface-epitopes.

3. An autoimmune model for CRPS

How can autoantibody-mediated autoimmunity in CRPS be understood? It should be noted that, although the CRPS signs and symptoms are limb-confined, patients have subtle systemic abnormalities, including mild autonomic dysfunction on tilt-table testing [26], and enhanced neurogenic inflammation in non-affected limbs [27]. We propose that limb injury creates an environment conducive to the binding of already circulating IgG serum-autoantibodies, to yet-unknown target structures (Fig. 1A). The post-injury environment would both facilitate autoantibody target access – e.g. by allowing extravasation, and break-down of the blood–nerve barrier – and foster the unravelling of hidden epitopes, or elicit changes in the conformation of target epitopes, such as in autoimmune conformeropathies [28].

As an important aspect of this conceptual model, any regional autoimmune pathology will not by itself cause the CRPS pain. The profound, weeks-lasting pain relief, which short acting intravenous low-dose ketamine (which resets spinal cord NMDA receptors, but has no important peripheral immune modulating effect) has in a majority of patients with longstanding CRPS [29,30], suggests that peripheral autoantibody effects are not directly noxious, but may rather act to enhance 'central sensitisation' (central sensitisation = the molecular process that corresponds to the clinical observation that after a period of intense or repeated noxious stimulation (a noxious stimulus actually or potentially causes tissue damage), innocuous (non-noxious) stimuli become painful and remain painful (for a while at least) even if the initial noxious stimulation has subsided) [31]. Further, the reduction in both pain and limb swelling effected by both brain training methods in early CRPS [32,33], and spinal cord stimulator (SCS) therapy in longstanding CRPS [34] also suggests that the regional CRPS pathology should be importantly contributed to by antidromic signals elicited from peripheral nerves (Fig. 1A).

4. Conceptual challenges

In order to advance our model, several conceptual challenges, described in this section, must be overcome. We provide some speculative answers, but further research is required before any firm conclusions can be drawn. If autoantibodies are indeed involved:

- *Why does CRPS preferentially affect peripheral limbs?*
  Susceptibility factors in peripheral limbs may include these regions' high density of sensory innervation, variant limb temperature, and a large cortical representation, when compared to other body parts.
- *How does the pathophysiology in those people with CRPS who recover early differ from other patients who have an extended course?*
  In early-resolving CRPS, serum-autoantibodies may only be present for a short time and then naturally reduce. A narrow window of vulnerability may exist, during which a trauma has the potential to trigger CRPS (Fig. 1B1). In other patients the autoantibody titres may not fully reduce, so that their noxious effect remains (Fig. 1B2), even after the initial limb signs have slowly resolved (see next paragraph).

– *Why do, in many patients' initial limb signs, such as swelling and colour changes reduce over time, whilst the pain remains?*
The early CRPS limb signs are often indistinguishable from the regular post-traumatic inflammatory tissue reaction. We suggest that in CRPS the normal post-traumatic immune activation is both augmented and prolonged through the activity of extravasating IgG serum-autoantibodies. This initial 'inflammatory' phase may facilitate the autoantibodies' access to the target organ(s); we suggest that access is then retained, even as the initial inflammation resolves (Fig. 1B2). As in any normal post-traumatic reaction, the initial post-traumatic CRPS reaction will eventually recede through normal resolution processes; such resolution may be accelerated with steroid treatment [35]. In longstanding CRPS, where patients often have severe pain, but fewer limb signs, serum autoantibodies continue to contribute to causing the patients' pain (Fig. 1B2); in these longstanding cases subtle 'inflammatory signs' are upheld by continuing autoantibody binding (Fig. 1B2).
– *How can brain training methods improve CRPS?*
Brain training methods can almost certainly reduce pain and limb swelling in early CRPS [32,33]. It would indeed be an exciting finding should autoantibodies be involved in those same patients, for whom disease signs can be lessened by brain training methods. The effect of these methods might be mediated through modification of the antidromic neuropeptide release from sensory nerves into the regional environment (Fig. 1A).
– *Why do patients with longstanding CRPS only rarely develop CRPS in a second limb after re-trauma, or operation?*
Serum-autoantibody titres may generally be lower in longstanding, than in early disease (Fig. 1B2), and/or in early CRPS the contribution of additional, situational and/or regional risk factors may also be essential. For example, as in other medical conditions, there is some evidence that patients with CRPS frequently experience major distressing life events in the year before CRPS onset [36] (but note psychological conditions are not more frequent in patients with CRPS before disease onset than in matched controls [37]). Some patients may also have had non-CRPS pain in the affected limb before their CRPS started, suggesting the possibility of additional regional vulnerability not present in other limbs (unpublished data).
– CRPS responds well to much lower IVIG doses-, and the time to maximal effect after IVIG treatment is shorter (3–5 days after a single infusion [38]) than in other IVIG-responsive autoimmune disorders: *why do patients with longstanding CRPS have such an unusual pattern of response to IVIG, and why does longstanding CRPS – most likely – not response to steroids?*
We'd like to suggest that unlike in other conditions autoantibodies involved in CRPS elicit much of their effect through a direct interaction with receptor functions, which is of quick onset and is quickly reversed by pharmacological interaction, rather than through slower processes of receptor turnover and/or complement mediated cell damage and/or attraction of neutrophils. The precise mechanisms of the IVIG therapeutic effect requires further study. Since that, which perpetuates CRPS it is probable not inflammation, it should not be treatable with steroids in anti-inflammatory doses.
– *If autoantibody binding is essential, why is there no tissue destruction?*
Although there is rarification of epidermal nerve endings, and additional minor changes, CRPS unlike some other autoimmune disorders is not associated with gross tissue destruction, suggesting that autoantibody binding does not initiate an immune cascade leading to cell destruction. Similar non-destructive patterns of receptor–autoantibody mediated autoimmunity are recognized in some forms or stages of both autoimmune encephalopathies [39] and autoimmune autonomic neuropathies [40]. In contrast, in classical receptor–autoantibody mediated diseases, such as acetylcholine receptor antibody-positive myasthenia gravis, the autoantibodies can activate complement and this leads to damage and structural changes at the neuromuscular junction.

5. Summary

Complex Regional Pain Syndrome is a chronic pain condition, which causes profound disability and an extraordinarily poor quality of life for many affected patients. Its causes have long been elusive, but recent research suggests, that CRPS may be a first chronic pain condition, for which causative autoantibodies will be established in a subgroup of cases. These results offer the prospect of developing both effective treatment strategies, and diagnostic and prognostic serum tests. Based on its clinical characteristics this condition should be considered a prototype of a new form of autoimmunity, which we propose to term 'Injury-triggered Regionally-restricted, Autoantibody-mediated autoimmunity with a Minimally destructive, course' (IRAM). Complex Regional Pain Syndrome, which had sometimes been considered psychogenic in the past, may in fact offer a novel model for our understanding of how 'functional' disorders, both painful and painless can be caused.

Take-home messages

- Complex regional pain syndrome (CRPS) is a painful post-traumatic condition for which no cure exists.
- Some patients with CRPS respond to IVIG treatment.
- A majority of patients with CRPS has IgG serum-autoantibodies directed against-, and activating autonomic receptors.
- CRPS may be caused by a new kind of autoimmune process.

Conflicts of interest

Dr. Goebel discloses the following potential conflict of interest: Dr. Goebel has been supported by the Pain Relief Foundation, Liverpool. He has received grant support from CSL-Behring and Talecris, and speaker honoraria from Baxter. Dr. Blaes discloses the following potential conflict of interest: F Blaes is supported by Bayer Healthcare and Grifols and received speaker honoraria from Grifols, Biogen Idec and CSL Behring.

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Anti-ganglioside antibodies are not useful as a serological marker of neuropsychiatric involvement in patients with systemic lupus erythematosus

Anti-ganglioside antibodies (AGA) have been proposed as putative serological markers of neuropsychiatric systemic lupus erythematosus (SLE), but recent findings are controversial. These autoantibodies are involved in the pathogenesis of several peripheral immune-mediated neuropathies. In order to investigate the potential role of AGA in neuropsychiatric SLE, Labrador-Horrillo et al. (**Lupus 2012;21:611-5**) tested the presence of AGA in the sera of a large cohort of consecutive SLE patients with or without active neurological involvement according to the 1999 ACR criteria for neuropsychiatric lupus syndromes. IgG or IgM AGA specific for different ganglioside antigens were detected by standard ELISA and confirmed by thin layer chromatography. AGA, mainly of the IgM isotype and specific for GM1 ganglioside, were exclusively found in about 30% of SLE patients with neurospychiatric involvement, but they did not correlate with any neurological manifestation in particular. Thus, the authors concluded that serum AGA are not useful as biomarkers of neurological complications in SLE patients.

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