

Current understanding of the causes of Complex Regional Pain Syndrome (CRPS), with its Medico-Legal Implications

Dr Andreas Goebel (pain medicine), PhD, FRCA FFPMRCA¹

Abstract

Complex Regional Pain Syndrome (CRPS) is a painful post-traumatic condition affecting limbs. About one in seven patients will not get better even at 1–2 years after the eliciting trauma, and for this group establishing the causation can be an important issue within a medico-legal context. Known CRPS risk factors such as female sex explain only a small fraction of the variability in developing the condition after trauma, whereas recent research has soundly rejected the idea of a pre-disposing CRPS personality. Although it is unknown what causes CRPS, there is no scientific evidence to support the idea that any trauma at any time would have anyway caused the condition. In the absence of firm evidence on causation it appears most logical to consider the particular trauma sustained at the particular time point as the most crucial element to the CRPS causation.

Keywords

CRPS, Complex Regional Pain Syndrome, medico-legal, pain

Background

CRPS typically develops after – often small – trauma to a peripheral limb.¹ About 9% of patients cannot recall any trauma, or report CRPS-onset following everyday activities such as jogging or typewriting.² Many people develop transient features of CRPS lasting for a few weeks particularly after fractures, which usually completely resolve.^{3,4} How is it possible that some patients develop a severe, lasting post-traumatic pain, given that these same patients, and indeed most of us experience small traumata many times in their lives without troublesome sequels?

The case

The only correct answer to this, from my perspective, is that *there is probably a reason, but we don't know it*. A popular default answer has been, for many years, that these patients have a psychological problem predisposing them to develop CRPS,⁵ but carefully conducted studies over the last five years have soundly rejected this option for the vast majority.^{6–8} Because of this strong refuting evidence, when patients *do* present with significant psychiatric, or psychological comorbidity, it should generally be assumed that this is either a chance coincidence (people with diabetes, for example, may also have psychiatric abnormalities, without suggestion of a link between their two problems), or that these psychological problems have

¹ Pain Research Institute, Department of Translational Medicine, University of Liverpool; and the Walton Centre NHS Foundation Trust, Liverpool.

developed in response to having CRPS; perhaps some patients are prone to react in that way to a major distress.

So if there is no 'CRPS personality', what else could there be causing this perplexing and sad condition? Clues come from a recent population-based study, the first of its kind, which has demonstrated associations between CRPS and female sex, asthma, migraines, osteoporosis and ACE inhibitor intake.^{6,9} Thus, it is possible that people, particularly females with either a hereditary or a medication-induced tendency to develop augmented neurogenic inflammation² after trauma, might be at risk.

Nevertheless, the facts that most patients will have experienced uncomplicated traumata before their CRPS-triggering event, and, independently, that only very few patients will develop a second episode of CRPS (2–3% of all cases²) suggest that these epidemiological results do not sufficiently solve the puzzle of the CRPS causation; i.e. the development of CRPS is still unpredictable, but there are known risk factors explaining a small part of the observed variability after trauma.

What are the implications of this current state of our knowledge in the medico-legal context? It appears that we indeed have to attribute causation to the specific trauma sustained. The alternative idea, that a patient would have developed CRPS 'anyway' with any subsequent trauma, would not appear logical given the usually unremarkable medical history as discussed above. It appears to be a logical approach if we assume that a majority of patients go through a 'time-window of vulnerability' created by unknown, mostly biological factors, and if a trauma occurs during this time, the risk for CRPS development is high: neither earlier, nor later trauma would then be equally detrimental. Thus, the trauma, occurring at the particular time at which it occurs should be important.

A novel twist to this story is provided by both ours and some other groups' recent research results.^{10–12} These results suggest that CRPS may in fact be a post-traumatic, regional, non-destructive auto-immune disorder, a prototype perhaps of a novel kind of auto-immunity.¹³ We hypothesise that an underlying auto-antibody-mediated auto-immune reaction, which is transient in the majority of patients, creates transient vulnerability to trauma. Transient auto-antibody-mediated disease is not uncommon in medicine (an example is Guillain-Barre syndrome); however, auto-antibodies here are usually understood to be both essential and sufficient to cause disease, while we suggest that, in CRPS, trauma is required in addition to a raised serum-auto-antibody level (i.e. auto-antibodies are essential, but not sufficient).

Most CRPS is transient (patients get better, although – with the exemption of those very early cases mentioned above – many will suffer important sequels), but in the medico-legal context chronic CRPS (patients whose pain does not get better at all) is probably more of a concern. We know now, from the same epidemiological study discussed above, that most patients will improve (although not necessarily fully

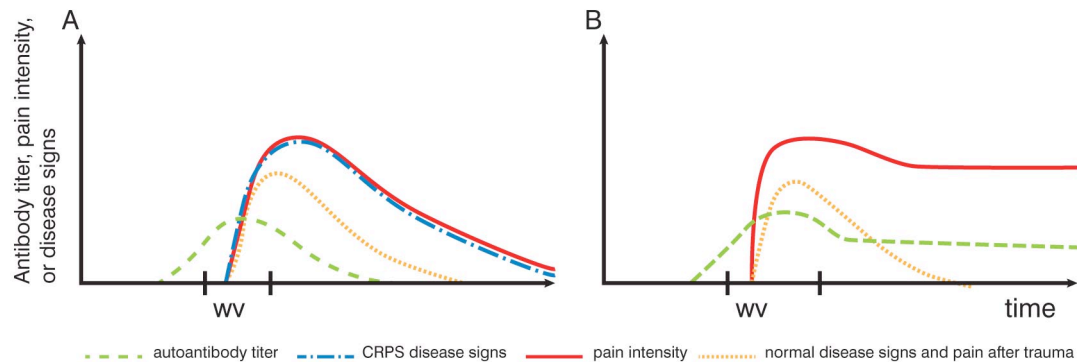
² 'Neurogenic inflammation' is an inflammatory response sustained by substances antidromically (i.e. against the normal course) released by peripheral sensory nerves. These substances include 'Substance P' (SP), and 'Calcitonin Gene Related Peptide' (CGRP) and others. The fact that CRPS is associated with ACE inhibitor intake (ACE inhibitors block neuropeptide metabolism), but not with the intake of any other antihypertensive medications further supports the notion of an important role of neuropeptides in CRPS. Neuropeptides cause swelling, reddening, and warmth, but other CRPS signs, such as sweating, can probably not be explained by their action and should have other causes.

recover) within the first 6–24 months after disease onset.¹⁴ Only one in seven patients will not improve by 24 months, and this group is less likely to quickly get better thereafter. How are these patients with chronic disease biologically different from those who got better? In order to answer this question, considerable research effort has focused on the idea that, as pain becomes chronic it may be mostly sustained by the brain, rather than by any peripheral (limb) processes. Thus, it is proposed, that in susceptible patients, after an initial painful peripheral traumatic insult, in the long run neural cell networks in the temporal brain lobe and elsewhere will retain an abnormal pattern of activity, sustaining a perception of pain; even so the peripheral insult has completely resolved. These ideas have gained further credence from the fact that in most patients with chronic CRPS limb disease signs, i.e. what we can see – swelling, colour changes, hair and nail growth changes, sweating – will reduce with time, while the only remaining abnormalities are often the patients' reported un-abiding pain and inability to fully move the affected limb.¹⁵ Thus, again, the idea here is that any original (if poorly understood) post-traumatic augmented peripheral inflammatory process reduces with time, and the central nervous system takes over. A Central Nervous System-sustained pain would resemble what has been shown in phantom limb pain^{3,16} Of note, this concept has not been proven in CRPS. Although patients with CRPS show substantial and important abnormalities, termed 'cortical reorganisation', in their brain's processing of peripheral signals, we don't know whether these processes are in fact hen, or egg, i.e. whether they really can sustain CRPS on their own, or whether they are themselves dependent on unknown on-going peripheral processes.¹⁷

Contrasting the popular idea of the importance of a central driver for long-standing CRPS, we suggest that in this group auto-antibodies are still essential pathogenetic elements: auto-antibody serum-titres will not recede, but these proteins will remain in the systemic circulation, similar as is the case in some chronic, auto-antibody-mediated auto-immune diseases, such as CIDP,¹⁸ but unlike in the acute auto-antibody-mediated auto-immune diseases such as Guillain-Barre syndrome where these auto-antibodies eventually disappear. These patients with long-standing CRPS may have an on-going, active auto-antibody-mediated immune process sustaining the clinical condition. In consequence, this process may in fact be treatable with immune treatments, even in very long-standing cases. Thus far, this is a largely unproven proposition. We have shown that some patients with long-standing CRPS respond dramatically with pain reduction to 'polyvalent immunoglobulin', an immune treatment, potentially supporting the idea.¹⁹

³ Phantom limb pain is pain in a non-existing arm, or leg, for example after traumatic amputation.

Figure 1



Simplified hypothetical relationship between autoantibody titre, CRPS disease signs, and pain intensity. A quickly resolving CRPS: if limb trauma occurs at a time (window of vulnerability, wv) where patients have a high titre of relevant serum auto-antibodies (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 autoantibody (AAB) titre naturally normalises, so do these CRPS features; *B* un-resolving CRPS: here, the auto-antibody titre only partially normalises, and while the initial post-traumatic reaction may slowly reduce through natural anti-inflammatory mechanisms, binding auto-antibodies continue to sustain the condition. Orange dotted line: normal course of swelling and pain after radius fracture. Adapted from reference 13, with permission.

Thus, auto-antibodies, after their first appearance in the body (presumed – as in other auto-immune diseases – to often occur after infections which abnormally activate the immune system) will then continue to be produced for a long time, or even indefinitely, and will sustain the CRPS clinical presentation. Although one might consider that once a person has acquired such serum-auto-antibodies, *any* trauma could elicit CRPS, the fact is, that even people with long-standing CRPS will only very rarely develop CRPS in a second limb after additional trauma. We propose that the level of auto-antibodies required to sustain CRPS is lower than that required to elicit CRPS after trauma (Figure 1 B). It appears we won't get away from the presumption that the incident trauma sustained at a particular time is probably essential for the CRPS disease process, and that even in these patients who develop long-standing CRPS, a trauma sustained three weeks later, or earlier, may not have had the same effect.

What, then, about those rare patients with chronic CRPS, who develop pain in additional limbs, without additional trauma (about 7% of cases²⁰) – can these additional problems really be attributed to the original trauma? First, in these cases it remains to be seen whether the now newly-affected limb is really affected by 'spreading' CRPS.⁴ The new Budapest criteria for CRPS have now been accepted by the International Association for the Study of Pain (IASP),²¹ and in consequence in order to confirm the CRPS diagnosis patients should have disease signs such as limb swelling or sweating; i.e. it is now not sufficient for making a diagnosis of spreading

⁴ 'CRPS spread' is the development of CRPS in body parts not initially affected; for example, where initially only one hand is involved, over time the whole arm and shoulder become affected ('proximal spread'), or other limbs become affected, either following additional trauma, or spontaneously.

when the patient reports such abnormalities to occur occasionally at home, while the doctor can't see them in clinic. In my experience, such signs are often not present in presumed 'spreading CRPS'. The Budapest criteria allow the use of the term 'CRPS NOS' ('not otherwise specified') in these cases. However, let's be clear that we are now talking about a very small subgroup within an already rare condition, and unfortunately little evidence exists to guide us. We can perhaps be forgiven, in the medico-legal situation, to be uncertain about the causation of any spreading in these cases.

Summary

As recent research evidence has helped us to nudge closer to gaining an understanding on the causes of CRPS, this has not changed the fact that the incident trauma at the specific time when it occurred should remain the single most important discernable causative factor for most patients; there is little support for a role of any CRPS-preceding psychopathology, or for the notion that just about *any* trauma sustained at *any* time would have caused the same condition. Watch this space ...

Conflict-of-interest disclosures

The author provides medico-legal reports for cases of post-traumatic CRPS for both plaintiff and defendant. He has received research support from CSL-Behring, BPL, Biotest, Talecris, Baxter and Grifols, Pfizer; travel support from CSL-Behring and Baxter; speaker honoraria from Baxter; and consultancy fee from Biotest.

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Correspondence

Dr Andreas Goebel, Pain Research Institute, Department of Translational Medicine, University of Liverpool, Liverpool L9 7AL

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