**Autoantibody Pain**

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**Abstract**

After autoantibody binding to target tissues, Fc-region dependent inflammation can induce pain by exciting nociceptors. But recently another possibility has emerged, whereby autoantibody binding to nociceptors can also directly cause pain, without inflammation. This occurs as a result of Fab-region mediated modification of nerve transduction, transmission, or neuropeptide release. In three conditions, complex regional pain syndrome, anti-voltage gated potassium channel complex autoimmunity, and chronic fatigue syndrome, initial laboratory-, and clinical trial-results have suggested a potential role for autoantibody-mediated mechanisms, with no or only little associated inflammation. More research assessing the pathogenic roles of autoantibodies in these and other chronic pain conditions is required. The concept of autoantibody-mediated pain offers hope for the development of novel therapies for currently intractable pain conditions.

**Keywords:** autoantibody, pain, complex regional pain syndrome, CRPS, VGKC, chronic fatigue

**1. Introduction**

The objective of this review is to highlight the topic area of ‘autoantibody pain’. It focuses on the emerging field of autoantibody-associated, non-inflammatory chronic pain conditions in the three examples of Complex Regional Pain Syndrome, anti-potassium channel-complex antibody associated pains, and painful chronic fatigue syndrome.

Chronic pain is a common human health condition that is associated with a poor quality of life [[1](#_ENREF_1)]. Most patients will, over time develop both pain-associated dysfunction, and psychological co-morbidity, so that chronic pain conditions incur high costs to the individual, their family, healthcare systems, and society as a whole [[2](#_ENREF_2)]. Recognition of the importance of chronic pain as a healthcare problem, and of the need to find effective management strategies has been rising [[3](#_ENREF_3)].

An understanding of the biological mechanisms underpinning chronic pain is required to develop effective pain-therapies, yet these mechanisms are often unclear. Although we don’t know how established demographic or psychosocial risk factors are translated into the development of chronic pain, these risk factors, and most structural tissue abnormalities, such as degenerative changes have in fact very little power to predict pain in an individual [[4](#_ENREF_4), [5](#_ENREF_5)]. On the other hand, using rodent models to better understand chronic pain has been challenging. These models won’t mimic the selective onset of chronic pain in humans, as most rodents develop significant persistent stimulus-evoked pain, but only a minority of human patients do so, after any given kind of injury [[6](#_ENREF_6)]. Thus the variable factors determining the development of human chronic post-injury pain cannot be fully understood from these models. Similarly patients can also develop chronic pain ‘out of the blue’, without any obvious preceding trauma or distress, a human observation of variability, for which there is no rodent model. Analgesic compounds developed using standard-injury rodent-models have unfortunately rarely been successful in clinical practice [[7](#_ENREF_7), [8](#_ENREF_8)]. Many of the drugs, which we use today to treat chronic pain, have rather small effect sizes, tolerance develops with long-term use, and their significant central side effects give much cause for concern [[9](#_ENREF_9)].

Thus today’s pain science cannot explain the development of chronic pain for an individual patient, and pain Specialists can frequently not treat them with an effective therapy.

The study of human genetic variants holds promise for both understanding the causes of pain variability, and developing novel analgesic treatments for chronic pain [[10](#_ENREF_10)]. But another recent approach to identify biological risk factors in chronic pain is the study of autoantibodies. An overview of the mechanisms by which autoantibodies may cause pain is given in Table 1.

Some autoantibodies are recognized as causing pain by inducing an inflamma-tory reaction, triggered by binding of complement to their Fc- region (Figure A, [[11](#_ENREF_11)]). Inflammatory mediators excite nearby intact nerve afferents sensing actual or potential tissue damage (‘*nociceptors*’, box), as the peripheral components of the pain pathway; the ensuing pain is termed ‘*nociceptive*’ (Box). Where such an inflammatory reaction also causes nerve cell damage[[1]](#footnote-1), *neuropathic pain* (box) may additionally arise (Figure A) [[12](#_ENREF_12)]. In contrast, where autoantibodies bind directly to nociceptors, causing either nerve-cell damage including as a consequence of complement binding, or causing a change in nerve-function, the resulting pain is primarily neuropathic.

Recent results have highlighted, that there is a group of chronic painful conditions, which are associated with i) no, or only minimal regional immune cell infiltration and tissue damage, ii) normal systemic inflammatory markers, and iii) specific peripherally binding serum-autoantibodies that activate cells in tissue culture. In these conditions, a minimal form of autoantibody-induced, complement-dependent inflammation may cause damage only to the bound cell-surface structures [[13](#_ENREF_13)]; alternatively, these autoantibodies’ pertinent pathophysiological action may include autoantibody Fab-region-mediated change of the function of the bound target (Table)[[13](#_ENREF_13), [14](#_ENREF_14)], such as:

i) direct modification of either function, or expression of receptors, or channels on nociceptors; the bound target may undergo conformational change, may be activated, or blocked, or cross-linked and internalized [[13](#_ENREF_13)]. In consequence, the nociceptor alters it’s transduction- or translation properties, or it’s pattern of neuropeptide secretion, so that it becomes more sensitive to noxious or non-noxious activation, or even spontaneously active and directly inducing persistant pain (Figure B). Inflammation is not required for these changes to occur. If ion channels are involved, then the disease-mechanism is termed an ‘autoimmune channelopathy’, paralleling known channelopathies with the lead symptom pain, such as erythromelalgia [[15](#_ENREF_15)].

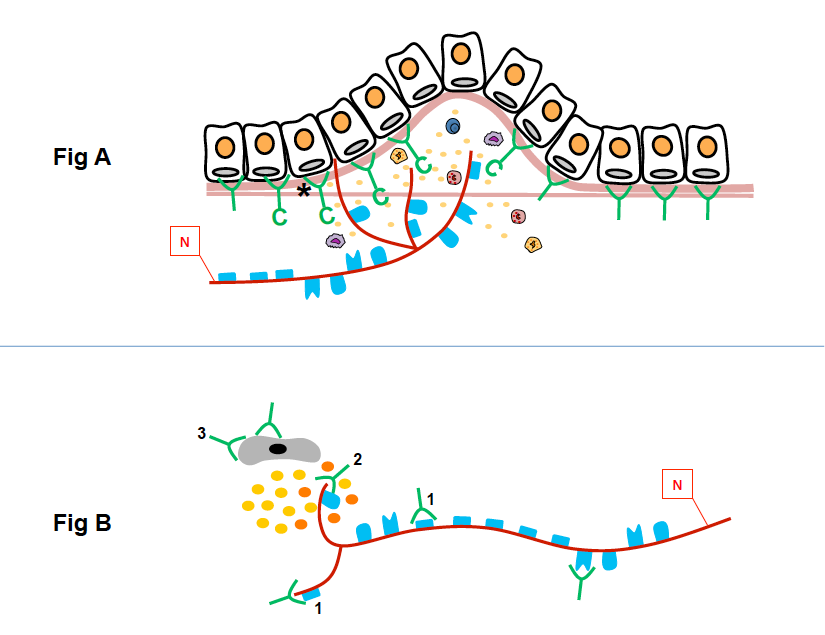
ii) modification of either function, or expression of receptors or channels in other cells such as sympathetic nerves, or keratinocytes, resulting in mediator secretion, and activation/ sensitization of nociceptors (Fab-mediated nociceptive pain, Figure B).

iii) induction of mild nociceptor damage; mild small fiber loss accompanies many chronic pain conditions [[16](#_ENREF_16)]; cell damage might activate/sensitise the surviving nociceptors [[12](#_ENREF_12)].

1.1. *Autoantibody pain arising after trauma*

Some chronic pains only arise after a patient’s exposure to physical-, or emotional trauma. In these situations, the pathogenicity of preexisting, circulating autoantibodies might be ‘switched on’ by the effects exerted by trauma-induced mediators [[17](#_ENREF_17)]. Alternatively novel autoantibodies may be produced as a result of the exposure of the adaptive immune system to trauma-released neo-antigens, or after trauma-induced loss of immunological tolerance (REF)

Figure



**Figure.** *Mechanisms of autoantibody-mediated pain*. ‘N’=nociceptor; **A**. In pemphigoid disease, autoantibody-binding to epitopes at the dermal-epidermal junction is followed by complement binding (‘C’) to the autoantibody Fc-region, which then induces inflammation leading to dermal-epidermal splitting (\*, only one epidermal layer shown). Inflammatory mediators (yellow dots) painfully excite nociceptors. Secondary neuropathic pain may arise from inflammation-induced nerve cell damage, including mechanical stretch between epidermal-, and dermal layers. **B**. An alternative kind of autoantibody-mediated pain depends upon Fab-region-mediated modification of the bound target. When binding to nociceptor surface receptors or channels (light blue), the autoantibody Fab-region directly alters neuronal fiber transduction/translation (‘1’), or neuropeptide release (orange dots) (’2’). Alternatively (‘3’) autoantibody Fab-region binding to peri-neuronal cells can trigger subtle release of inflammatory mediators (yellow dots), that can excite nociceptors.

Table

|  |  |  |  |
| --- | --- | --- | --- |
| Mechanism of autoantibody-pain | | Pain classification | Disease example |
| Fc | Binding to non-neuronal, cells; Fc-region triggered inflammation leading to i) sensitization/ activation of nociceptors by inflammatory mediators, plus possibly ii) damage to nociceptors as result of the inflammation. | I) Nociceptive, plus ii) possibly neuropathic | Bullous pemphigoid |
| Binding to neurons, or glia; Fc-region triggered complement activation and (potentially minimal-) inflammation leading to neuronal damage. | Neuropathic | Guillain-Barre-Syndrome [[18](#_ENREF_18)];  Neuromyelitis optica [[19](#_ENREF_19)]  ? CRPS  ? VGKC-associated pain  ? Chronic Fatigue Syndrome |
| FabF  Fab | Binding to nociceptors; Fab-region mediated modification of the bound target, including: i) binding-site blockade, ii) alteration in the target conformation, iii) target activation, iv) target-crosslinking with internalization, v) altered neuropeptide secretion from the nociceptor. | Neuropathic |
| Binding to cells in the nociceptors’ vicinity; Fab-region mediated change in cell signaling such as increased mediator secretion consequently activating and/or sensitizing nociceptors | Nociceptive |

Table: *Mechanisms of autoantibody-mediated pain*. Note, in predominantly Fc-region mediated conditions, additional Fab-mediated effects may contribute, and vice-versa. ?= unconfirmed.

Some pain conditions are additionally associated with muscle pains and cramps, typically resulting in response to the experience of severe pain, or as a result of the inability to exercise. Fc/Fab= pain mediated by the autoantibody Fc/Fab region. ‘Nociceptor’=nerve cell, which responds to potentially or actually tissue damaging stimuli.

**2. Results and Discussion**

*2.1 Complex Regional Pain Syndrome (CRPS)*

CRPS is a post-traumatic pain affecting distal limbs, which is associated with regional autonomic signs, and mildly reduced small-nerve fiber density [[20](#_ENREF_20)]. The condition can be severe. Systemic inflammatory markers are normal. There are increased concentrations of tumor necrosis factor alpha and interleukin 6 in the interstitial fluid of the affected skin. Thee concentrations of these mediators does not correlate with the patients’ pain intensities, and they normalize by 6 month after disease onset, including in patients with ongoing severe pain and autonomic signs [[21](#_ENREF_21)]. In the affected skin, there is also an early, transient increase in mast cell numbers, but there is no immune cell infiltration [[22](#_ENREF_22), [23](#_ENREF_23)]. About 15% of patients do not improve within 12-18months, and these patients usually retain the condition. Patients with such chronic CRPS report amongst the lowest quality of life scores in medical diseases [[24](#_ENREF_24)]. In almost all other patients the condition is monophasic – it does not return once it has resolved [[25](#_ENREF_25)].

Autoantibody contribution in CRPS has recently been reviewed in this Journal [[26](#_ENREF_26)], and additional findings have since been published. Indications for an autoantibody role first came from the observation that some patients appear to respond to immunoglobulin treatment. This was followed by laboratory studies showing enhanced binding of patient serum to both autonomic-, and sensory nerves. In CRPS immunoglobulin G passive-transfer experiments, intact animals exhibited abnormal behavior. Recently three specific immunoglobulin G-autoantibodies that activate autonomic receptors have been described, directed against beta 2, muscarinic 2, and alpha 1a receptors [[27](#_ENREF_27)]. Incubation with CRPS serum immunoglobulin G induces changes in vascular endothelial and smooth muscle cells, and in bone cells, possibly providing an explanation for micro-vascular and osteoporotic changes in patients with early CRPS [[28](#_ENREF_28)]. CRPS serum-immunoglobulin G transfer to hind-paw injured animals elicits relevant aspects of CRPS, including mechanical hyperalgesia and swelling restricted to the injured paws [[17](#_ENREF_17)]. Cultured dorsal root ganglion cells incubated with patient immunoglobulin G change their calcium handling, but only if they were first exposed to ‘inflammatory soup’ [[29](#_ENREF_29)]. The latter two observations are consistent with the idea that CRPS serum-autoantibodies become pathogenic in the context of tissue-inflammation. Additional studies are required to clarify relevant antibody target-epitopes, the mechanisms through which injury becomes a prerequisite for development of the disease, and the pathways by which patients can retain pain, long after the injury is settled.

The importance of central sensitization (box) in CRPS is suggested by excellent responses of many patients to prolonged low-dose infusion with the NMDR-receptor antagonist ketamine, and delayed pain increase after the infusion is stopped [[30](#_ENREF_30)]. Thus antibodies might work by subtle changing of peripheral nerve function producing a slow build-up of central sensitization.

Corresponding with these laboratory findings, several clinical teams have treated longstanding CRPS with immune modulating therapies. Positive studies of intravenous immunoglobulin treatment have been published, including one small randomized controlled trial [[31](#_ENREF_31), [32](#_ENREF_32)], and both we, and others have also reported initial evidence, that therapeutic plasma exchange and anti-rheumatic drug treatment might be effective [[33-36](#_ENREF_33)]. Use of pharmacologic B-cell ablation has not yet been reported. Placebo-responses in long-standing CRPS are typically small [[35](#_ENREF_35)], nonetheless, as always large prospective trials are required to confirm the efficacy and effectiveness of immune therapies in clinical practice.

*2.2 Potassium channel complex antibody-associated chronic pains*

Potassium channels are involved in regulating peripheral nerve excitability [[12](#_ENREF_12)]. Immunoglobulin G-autoantibodies binding to the Voltage-Gated Potassium Channel (VGKC) complex are prevalent in neuromyotonia, a condition characterized by motor nerve hyper-excitability, and additionally in very rare disorders [[37](#_ENREF_37)] [[38](#_ENREF_38)]. In neuromyotonia, these autoantibodies crosslink VGKC-complexes, leading to receptor internalization, reduced K+ currents, and increased nerve excitability [[39](#_ENREF_39)].

Pain has only recently been investigated in VGKC-complex autoantibody associated disorders. Irani and colleagues first reported that pain is an important feature of anti-VGKC-complex autoantibody-associated neurological disease; their data also indicate, that pain might be particularly common, when the autoantibody target is Contactin-associated protein 2 (Caspr 2), a molecule which is complexed with the actual channel subunits [[40](#_ENREF_40)].

Anti VGKC-complex autoimmunity may cause pain independent of overt neurological disease. Meeusen et al. report the case of an abattoir worker, who had become exposed to aerosolized swine brain tissues [[41](#_ENREF_41)]. Although this patient had the highest concentration of anti VGKC-complex antibodies (CASPAR negative in this case) amongst a group of similarly exposed patients presenting with sensory polyradiculopathy, strikingly her presentation was characterized by only few ‘hard’ neurological signs. Her lead symptom was severe neuropathic pain, which initially affected the lower extremities, but later spread to involve both trunk, and upper extremities. Weekly high-dose intravenous immunoglobulin treatment initially resulted in excellent pain reduction, yet therapy-cessation caused her pain to return each time; later the patient stabilized on methotrexate and bi-weekly high-dose intravenous immunoglobulin treatment.

Klein and colleagues, from the same author-group, at the Mayo clinic subsequently reviewed the notes from 316 patients referred with various neurological complaints and neurologically examined at that center, who were VGKC-complex immunoglobulin G positive. The group was a sub-group of a larger group of patients, whose serum had tested VGKC-complex positive over two years at this centre’s supra-regional reference laboratory; i.e. this group of 316 included patients with diagnosed neurological disease, but also other patients who had no neurological signs on examination. Disease controls were patients with other anti-neuronal autoantibodies [[42](#_ENREF_42)]. Multivariant analysis showed that positive VGKC-complex Immunoglobulin G status, and specifically CASPAR2-IgG sero-positivity correlated significantly with pain prevalence. In patients who complained about pain (n=159), extremities were most commonly affected, and a third had total body pain. Of note, prior to referral pain had been diagnosed as ‘psychogenic’ in 13% of these 159 patients. Pain had been the first presenting symptom in almost all of these patients, and 45 of the patients (28%) had pain as their sole complaint at presentation. The findings provide preliminary support for the proposition, that anti VGKC-complex autoimmunity, and particularly anti CASPAR2-autoimmunity may be a cause of chronic pain. Unlike in the abattoir workers, markers of a systemic inflammatory response were not reported in this group of 316 patients. Of note, when we tested our patients with longstanding complex regional pain syndrome for VGKC-complex autoantibodies we obtained consistently negative results (Goebel and Vincent, unpublished observations); there were also no patients with complex regional pain syndrome amongst those 316 patients reported by the Mayo group.

Pain in VGKC-complex autoantibody-associated conditions should perhaps be transferable via passive transfer, but to date no behavioral data have been published.

Klein et al. treated their VGKC-complex seropositive patients, including cases ‘only’ presenting with pain, with various immune modulation therapies, and they noted pain improvements in a majority. Prospective studies are required to enable clinicians to rationalize both serum-testing for anti VGKC-autoantibodies, and immune modulation treatment for seropositive patients complaining predominantly about pain; the designs of any such studies will need to take into account that such presentations are likely to be very rare [[43](#_ENREF_43)].

*2.3 Chronic Fatigue Syndrome*

Much less is known about a possible autoantibody contribution in this condition, as compared with the other two discussed clinical syndromes. Recent laboratory and clinical results have provided a signal indicating that this topic should be further investigated. Chronic fatigue syndrome (CFS) is commonly defined as severe fatigue lasting longer than 6 months, associated with at least four out of eight possible additional symptoms (Fukuda criteria [[44](#_ENREF_44)]). Of these eight symptoms, four are painful: new headaches, multiple joint pains, muscle pain, and tender lymphnodes. The pain quality in CFS is mostly aching, considered reflective of a muscle-related origin. A recent report from a consensus group under the umbrella of the Institute of Medicine suggests a new name for the condition, ‘Systemic Exertion Intolerance Disease’, with pertinent diagnostic features not including pain [[45](#_ENREF_45)]. Notwithstanding, there is agreement that in addition to fatigue, painful symptoms are frequently central to patients’ experiences of the condition [[46](#_ENREF_46), [47](#_ENREF_47)]. The etiology of CFS is unknown, and better therapies are urgently required [[48](#_ENREF_48)].

In laboratory tests, a variety of serum-autoantibodies, including functionally active anti-autonomic antibodies have been described in subgroups of patients with chronic fatigue syndrome [[49](#_ENREF_49)], however passive-transfer- or immunization-studies have not yet been published.

Recent results have suggested that a subgroup of patients with CFS may respond to treatment with Rituximab, an anti CD-20 biologic, which ablates both pre B-cells and mature B-lymphocytes. An initial small, randomized controlled trial investigating the effect of one treatment cycle, and designed to have its primary outcome at 3 months, was negative, although rapid B-cell depletion was confirmed. Post hoc analysis suggested substantial improvements during the follow up period, with maximal fatigue-, and pain relief between 6-12 months after the infusion in the intervention-, when compared with the control group [[50](#_ENREF_50)]. The authors hypothesized that this slow effect-onset might relate to pathogenic activity of mature B-cells. It is known that Rituximab might not target this cell-type as well as it targets more short-lived cells [[51](#_ENREF_51)]. As Rituximab effectively targets precursor cells, a longer treatment period may be required until the number of mature plasma cells is reduced through natural cell death. In a subsequent, open study investigating repeated Rituximab infusions-cycles, significant improvements including a reduction in pain intensity were again observed with a delayed onset from 6 months after the first infusion; maximal effects were noted between 15-24 months. Fifty percent of patients in the intervention group had a major improvement in their fatigue scores [[52](#_ENREF_52)]. Interestingly, during follow-up, after treatment had stopped, patients often had prolonged responses, far exceeding the 6-month time period to B-cell reconstitution. A large randomized controlled trial investigating repeated treatments over 15 months has now completed enrollment, with results expected for 2017 (clinicaltrials.gov/ct2/show/ NCT02229942). In contrast, two recent, large Rituximab trials in Sjoegrens syndrome with fatigue as primary outcome, had negative results (REF).

**3. Conclusions and outlook**

Autoantibody-mediated pain is a novel disease concept, which may explain the variability behind the occurrence of certain severe chronic pain conditions. There is evidence, that chronic pain conditions can be associated with specific, cell surface-receptor activating immunoglobulin G autoantibodies. Increased pain sensitivity can be transferred from patients with complex regional pain syndrome to rodents, by injecting the animals with patients’ immunoglobulin G. There is also initial evidence for the efficacy of immune modulating treatments for certain chronic pain conditions.

The nature of autoantibody target epitopes, and how their binding may cause chronic pain remains unknown. The apparent absence of inflammatory cell infiltration in longstanding chronic pain conditions renders both Fc-region dependent rarification of surface receptors, and Fab-region dependent modulation of the bound targets interesting potential mediating mechanisms. Studies to further clarify these effects are required.

Given that common pain conditions, such as Fibromyalgia Syndrome appear to sometimes respond to immune modulation treatment, assessment for an autoantibody contribution in these conditions would appear timely [[53](#_ENREF_53), [54](#_ENREF_54)].

The concept of autoantibody pain offers hope for the development of new types of analgesic treatments. Such treatments may reduce autoantibody concentrations, interfere with either target epitopes or directly with pathogenic autoantibodies, or perhaps enhance compensatory effects paralleling cholinesterase inhibition in myasthenia.

Since pain is considered a ‘biospychosocial’ condition [[55](#_ENREF_55)], the contribution of psychological and social factors will require further study: one wonders whether it is possible that in some instances the brain, perhaps in response to distressing experiences can contribute towards activating the B-cell response.

**Take-home messages**

* Autoantibody binding to self-epitopes can cause pain through Fc-region triggered inflammation
* Autoantibody Fab-region binding may directly induce painful change of neuronal function, without causing overt inflammation
* Initial evidence for autoantibody pain exists in three specific chronic pain conditions
* Immune modulation therapies may be effective to treat autoantibody pain

**Conflicts of interest**

Dr. Goebel discloses the following potential conflicts of interest: Dr. Goebel has been supported by the Pain Relief Foundation Liverpool, the David Hammond Foundation, and the Great Britain-Sasakawa Foundation (Research Charities). He has received grants from Biotest, consultancy fees from Biotest and Axsome, and a speaker-honorarium and travel support from CSL-Behring.

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**Box**

*Nociceptor*

A nerve cell, which responds to actually or potentially damaging stimuli

*Nociceptive pain*

Nociceptive pain develops when receptors on intact nerves, which can sense noxious signals (a noxious signal actually or potentially causes tissue damage) are excited, for example through exposure to inflammatory mediators released under a skin blister (http://www.iasp-pain.org/Taxonomy?navItemNumber=576#Nociceptivepain).

*Neuropathic pain*

This is pain arising as a direct consequence of a lesion or disease affecting the somatosensory system [[56](#_ENREF_56)]. Examples include pain after partial nerve transection, or pain as a result of diabetes-associated metabolic nerve damage, or chemotherapy-induced nerve damage. For clarity, although neuropathy is frequently diagnosed upon a reduced count of small skin nerve fibres, the mere rarification of nerve fibres cannot explain the development pain, and ultimately what makes a condition painful on the background of an established noxious triggers is often not known. Genetically-determined variations in the abnormal expressions of channels in response to nerve-fibre damaging events (which do not necessarily need to destroy these fibres) is one attractive possibility that is currently subject to intensive research [[57](#_ENREF_57)].

*Central Sensitisation*

Central sensitization is the molecular process that corresponds to the clinical observation that after a period of intense or repeated noxious stimulation, innocuous (non-noxious) stimuli become painful and remain painful (for a while at least) even if the initial noxious stimulation has subsided [[58](#_ENREF_58)]. This mechanism is important in most chronic pains. In the context of autoantibody-pain, the noxious stimulation might be the autoantibody-mediated activation of small nerve fibers.

1. ‘damage’ is defined here as an alteration of either nerve function, or nerve structure, which is not dependent on the continuous presence of the pathogenic element; for example nerve exposure to inflammatory mediators may induce lasting changes in nerve receptor expression, which continue even if the inflammation resolves (REF). [↑](#footnote-ref-1)