**The Biology of Symptom-Based Disorders – Time to Act**

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**Abstract:** Symptom-based disorders are conditions that are characterised mostly by somatic symptoms rather than objectively identifiable signs. They are very common, including pain and fatigue disorders, functional gastrointestinal and respiratory disorders, and others, and they cause far greater disability than diseases where signs are prominent. Such conditions may sometimes be triggered by infection, as in Post Covid Syndrome 1,2 or physical or psychological trauma. By employing passive immunoglobulin transfer experimental approaches, recent research in several ‘unexplained’ chronic pain conditions has demonstrated that pathogenic IgG autoantibodies can explain several of these conditions’ core symptoms and are ubiquitous in patients with severe phenotypes. The promise from placing positive resources into exploring the role of ‘invisible’, functional, non-inflammatory autoantibodies in symptom-based disorders across additional areas of Medicine includes patient empowerment and the development of new diagnostic tests and therapies.

**Main Manuscript Text:** Symptoms are experiences that patients report to their health care professionals. ‘Symptom-based disorders’ can be defined as conditions characterised mostly by somatic symptoms, rather than objectively identifiable signs3. Such conditions are very common and cause far greater disability than diseases where signs are prominent4. Unfortunately, the underlying causes of symptom-based disorders are typically not understood, and there are few effective treatments.

Should one classify symptom-based disorders the list would be long. It would include, in addition to pain and fatigue disorders, postural tachycardia syndrome (POTS)5, idiopathic tinnitus, ‘functional’ dyspnoea, functional sleep disorders, functional gastrointestinal disorders6, and others. Subtle signs such as small nerve fibre pathology7-10 or autonomic dysregulation11,12 may occur, but their importance is dwarfed by the impact of the symptoms 13,14.

The recent COVID epidemic has brought symptom-based disorders into sharp focus. Following resolution of acute COVID infection, many people report debilitating somatic symptoms such as fatigue, ‘brain fog’, pain, and dyspnoea, with few accompanying signs. These symptoms are labelled Post Covid Syndrome (PCS)15,16 and, as is common in symptom-based conditions, PCS is often also associated with mental symptoms such as anxiety.

AG, DA and others have recently identified potential aetiological factors for unexplained *painful* symptoms. We have demonstrated a change in neuronal communication produced by functional, non-inflammatory autoantibodies. In Fibromyalgia syndrome (FMS), Complex Regional Pain Syndrome (CRPS), and other chronic pain conditions, autoantibodies enhance the impulse activity of peripheral sensory afferent fibres, without evidence of tissue destruction or inflammation17,18. In each of these disorders, proof of functional consequences of the respective autoantibodies was achieved by injecting purified patient antibodies into mice, a method termed ‘passive immunoglobulin transfer’. In some instances, a ‘double hit’ was required; for example, in CRPS, an uncommon post-traumatic limb pain condition, paw trauma was an obligatory component, and the transferred symptoms remained restricted to the injured paw19-22. No additional insult or trauma was required to transfer FMS symptoms, where IgG transfer elicited widespread symptoms. The discrepancy between CRPS and FMS also confirms that the nature of functional autoantibodies differs between these conditions. Following administration of patient IgG these rodents developed typical disease features such as hypersensitivity to mechanical pressure or cold and reduced grip strength that were specific to the respective patient donor’s disease phenotype. We only assessed severely affected patients, and we unexpectedly found for each examined condition that functional antibodies were ubiquitous, meaning that these results satisfy Witkeby’s criteria for autoimmune aetiology for (at least) the severe manifestations23. Preliminary results suggest that abnormal autoantibody production typically accompanies PCS, but confirmation of a causative link is outstanding1,2,24.

Such symptom-based disorders often follow a recognised trigger, such as an infection25,26 or trauma - which can be physical or psychological27. One putative explanation for psychological trauma has been that the brain *expresses* present or past distress as abnormal symptoms, i.e. a form of hysteria, or that such distress may establish a state of central sensitisation, which amplifies normal sensory experiences into pain.28 The addition of the autoantibody findings, however, suggest that distress can trigger symptomatic immune activation (Figure 1).



**Figure 1***. Paradigms for the translation of distress into symptoms.*A) triggered by distress the brain generates abnormal symptoms (hysteria, somatisation); B) either experience of distress, or alternative triggers initiate the production of functional autoantibodies causing symptoms.

For established autoimmune disorders, integrating his and others’ findings YS has proposed the conceptual framework ‘*hyperstimulation by environmental factors in genetically susceptible individuals’*, outlining how various triggers may converge (Figure 229). External stimuli include hormones, infections (including COVID-1930), adjuvants such as silicone breast implants13,27, and novel cancer therapies with check points inhibitors. He espoused the view that genetic predisposition31 largely determines whether an individual will develop *classical* autoimmune disease; in particular the HLA-DRB1 gene, which may be “notorious” for its links to autoimmunity29,31.

Such classical autoimmune diseases are often also associated with chronic widespread pain, and fatigue. However, whether trigger- and genetic factors for autoantibody-mediated symptom-based disorders i.e., disorders without destructive phenotypes are unique from those in classical autoimmune disorders, and how infection or distress translate into autoantibody production in these disorders must require explorative work.



***Fig.2.*** *Hypothesis about the development of classical, established autoimmunity through hyperstimulation from environmental factors in genetically vulnerable people*

Results from recent chronic pain research suggest that hitherto invisible immune mechanisms may manifest in debilitating symptom-based disorders. Functional, non-inflammatory autoantibodies are not detected by modern proteomics, metabolomics, or transcriptomics studies and might represent a yet-unexplored regulatory system of the body. It would seem prudent across additional areas of medicine to place effort and positive resources into exploring the role of functional autoantibodies, their trigger factors, and their potential evolutional purpose. The promise from such research initiatives includes patient empowerment, and development of new therapeutic or preventative interventions which may yield needed cost reductions for our social and healthcare systems. Now is an apt time to act!

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