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Opinion

Spikeopathy and PACVS: the gift that keeps giving. An opinion piece

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While most people recover well from acute COVID-19, a significant subset go on to develop 'long Covid' (PACS), defined it as "an infection-associated chronic condition (IACC) that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems".[1]

A smaller but significant group develop a similar syndrome post COVID-19 vaccination, with no evidence of any COVID-19 infection either on clinical history, or serology. This entity is now termed Post-Acute COVID-19 Vaccination Syndrome (PACVS).[2] Indeed, most cases of PACVS occur in vaccinated populations as the vast majority of the Western population has been vaccinated. The disease burden from PACVS is potentially large, and demonstrably underreported as a result of significant failures in pharmacovigilance, with credible estimates of between 0.2 to 0.9% of COVID-19 vaccine recipients developing the condition.[3]

PACS and PACVS share substantial symptom overlap, including profound fatigue, post-exertional malaise (PEM), brain fog, dysautonomia (particularly Postural Orthostatic Tachycardia Syndrome or POTS), sleep disturbances, small fibre neuropathy, and ME/CFS-like features.[4] Both are consistent also with chronic sympathetic nervous system activation and dysfunction of the cholinergic anti-inflammatory Pathway (CAP).[5] Both can lead to significant disability, with many patients becoming housebound or bedbound.

Clinically, PACVS presents as similar to the myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) cluster. Other overlaps with existing syndromes include POTS, mast cell activation syndrome (MCAS) and small fibre neuropathy (SFN). Symptomatically, PACVS is characterized by dysautonomia, post-exertional malaise, fatigue, and often accompanying neuropathic pain and cognitive disturbances, such as brain fog.[4]

Spike protein is known to be pathogenic, whether from acute COVID -19 or from vaccination[6] and has been demonstrated to persist for some years post vaccination, in some Long Covid[7] and some PACVS cases as presented here. Spike protein is well known to bind to the ACE-2 receptor as its primary point of entry: however, it also binds to numerous other receptors resulting in effects on numerous cell types and triggering numerous cascades. In addition, the spike protein is directly toxic to endothelial cells, myocardial cells, neurons and mitochondria to name a few, resulting in endotheliitis, platelet and immune cell activation, micro thrombi and micro amyloid formation, tissue mast cell activation, neutrophil activation and the formation of neutrophil extracellular traps (NETOs) is and mitochondrial dysfunction.[6] These then trigger hyper inflammation, reactive oxygen species (ROS) and further tissue damage. As the spike protein also binds to and downregulates a-7n AChR, the Cholinergic Anti-inflammatory Pathway 'brake' system for sympathetic nervous system driven inflammation fails.[5]

The spike protein is also able to penetrate the blood brain barrier and gain access to the central nervous system via several mechanisms and again is directly neurotoxic. It is recognised as a Pathogen- Associated -Molecular -Pattern (PAMP) and thus triggers microglial activation, the release of cytokines and inflammasomes and neuroinflammation. It is also directly toxic to the mitochondria resulting in damage to the succinic acid dehydrogenase complex in the respiratory transport chain, impaired ATP production and increased ROS; this then triggers ongoing inflammation and impaired purinergic signalling from abnormal levels of extracellular ATP which further acts as danger signals.[8]

In addition, the spike protein is able to directly and rapidly cause mast cell degranulation both peripherally and centrally, adding further fuel to the proinflammatory fire and creating Mast Cell Activation Syndrome as part of the spectrum of spike protein induced pathology.[9]

Of particular interest in PACVS is the repeated finding of G-protein class receptor (GPCR) autoantibodies (AAB).[10] Unlike typical Ig G antibodies which create tissue damage and destruction, these are functional AAB which bind to their target receptors and create ongoing agonist or antagonistic actions. The commonest of these AAB in PACVS are against the ACE receptor, b2 adrenergic receptors and MAS-1 receptors; it has been noted that autoantibodies to AT1R, ETAR, b2-adr-R, M2R, MAS-1, IL-1-Rb and IL-6 were all highly sensitive (64 to 90%) and predictive of PACVS as compared to post vaccination subjects.[11]

GPCR are the largest superfamily of integral membrane proteins in humans and it is thought that these autoantibodies are natural components of human biology[12] and that GPCR-specific autoantibody signatures are associated with physiological and pathological immune homeostasis.[13] Classical AABs targeting Angiotensin II (AngII), Angiotensin Converting Enzyme 2 (ACE2) and MAS1 oncogene (MAS) receptors have been frequently observed in acute COVID-19 patients,[14] and appear to correlate with the severity of symptoms both in acute COVID and post Covid conditions.[15] The high intensity immune response to acute spike protein exposure may also contribute to the production of GPCR AAB, potentially by molecular mimicry,[16] as the spike protein has a significant homology with many human epitopes.[17] These GPCR-AAB persist, acting as pathogenic agonist

AABs by inducing a chronic activation of the target receptors, with resultant chronic sympathetic nervous system activation, receptor overstimulation, increased intra- and extracellular oxidative stress and endothelial dysfunction inducing a pathogenic cycle of inflammation and ischaemia.[16] Resultant dysfunctional microcirculation has been visualised in retinal capillaries in the presence of GPCR AAB against adrenergic β2-receptor, MAS-receptor angiotensin-II-type-1 receptor, and adrenergic α1-receptor, consistent with this cycle of pathogenicity.[18]

Spike protein has been demonstrated also to be pathogenic to colonic bacteria with a loss of commensal bifid bacteria post vaccination.[19] This alteration in colonic bacterial pattern will further drive autoimmune profiles and perpetuate the pattern of immune dysfunction and inflammation.[20]

The interplay of these factors is illustrated in 2 cases, both previously fit and healthy young men in their 30s, triggered into acute ill-health by COVID-19 mRNA vaccination.

I. Mr B developed acute pericarditis confirmed by 2 cardiologists. He progressed to develop chronic pericarditis, burning sensations around the chest and symptoms cluster overlapping predominantly with ME/CFS. Investigations revealed high d-dimer and homocysteine, high persistent spike protein levels 3 ½ years post vaccination, with negative nucleocapsid antibodies, positive plasmid DNA in PBMC, high GPCR AAB in the demonstrated pattern, mitochondrial dysfunction on urinary amino acid testing consistent with a block at succinic acid dehydrogenase; colonic dysbiosis with loss of bifidobacteria.

II. Mr K developed acute multisystem symptoms with prominent dysautonomia, neurological and neurocognitive symptoms post his first COVID-19 mRNA injection, with slight recovery before he received his second injection and then deteriorated markedly such that he has been predominantly housebound since. He has had numerous ED admissions two of which were for tachycardia and was treated for AF.

He has demonstrated numerous abnormalities on testing including extremely high spike antibody, but negative residual spike protein or nucleocapsid antibody; high nucleolar pattern ANA; high GPCR AAB; nerve biopsy positive for Small Fibre Neuropathy; NASA lean test positive for POTTS and dysautonomia; Neuroquant volumetric MRI demonstrating widespread changes in volume, predominantly in basal ganglia, hypothalamic regions, enterorhinal cortex reported as consistent with microglial activation; abnormal urinary organic acids profile consistent with mitochondrial dysfunction and block in the succinic acid dehydrogenase complex; colonic dysbiosis with loss of bifidobacterium. He was symptomatically improved for sodium cromoglycate indicating mast cell activation.

In both of these young men, abnormal functional autoantibodies are demonstrated at high levels, in patterns consistent with dysregulation in neurological, cardiological and microvascular function, in the absence of evidence of acute COVID-19. While one has persistent spike protein, the other does not, indicating that the spike protein pathogenicity is being perpetuated by the anti-spike antibody itself and by the GPCR AABs not simply by persistent spike protein. Indeed high spike antibody levels have been demonstrated to directly correlate with anti -ACE-2 antibodies, and anti- ACE-2 Ab positive patients have a four-fold risk of increased symptomatology compared to ACE-2 Ab negative ones.[10]

As the spike protein has such widespread pathogenicity it is of no surprise that the clinical manifestations are so protean. Although only a small proportion of vaccinees go on to develop PACVS, neurological and cardiological symptoms are the commonest side effects reported post vaccination,[4] and it may well be that many cases with GPCR AAB and thus effectively an autoimmune self -perpetuating condition, are going unrecognised and untreated.

To date there is no one clear effective therapy for PACVS: but as there are many demonstrable abnormalities, so there are many possible avenues for intervention. This is a topic for further investigation.

For further discussion on the above issues, the paper '**Spikeopathy and PACVS: The Putative Role of the Spike Protein Illustrated in Two Case Histories' is currently in review process.**

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None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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