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Diagnostics and therapy for post-COVID-19 and post-vaccination syndrome

A field report from Havelhöhe Hospital Berlin

Introduction

Post-COVID-19 (PCS) and post-vaccination syndrome (PVS) refer to complex and multi-layered clinical pictures that can occur after an acute COVID-19 infection or vaccination against SARS-CoV-2. The clinical presentation is diverse: it includes symptoms such as fatigue, cognitive impairments (brain fog) and autonomic dysfunctions.

> "In Germany, it must therefore be assumed that 600,000 to 1.4 million people affected

There are unanswered medical questions and considerable social tensions regarding both syndromes: There is still no consensus on the disease entity and pathogenesis. The ICD coding (International Statistical Classification of Diseases and Related Health Problems) as a merely supplementary diagnosis (U09) is also disputed. The clinical picture is often interpreted as a somatofor- mal disorder and thus categorised as a mental/psychological disorder. In the meantime, much is known about an immunological pathomechanism and the role of the spike protein and this has become the basis of our therapeutic concepts.

There is a considerable burden of disease for those affected. It must therefore be assumed that 600,000 to 1.4 million people are affected in Germany. In the last 12 months, we have treated around 600 patients with post-infectious fatigue syndrome and received a total of over 1800 enquiries about PCS and PVS. However, those affected do not encounter a generally sufficient or appropriately differentiated care structure. Specialised diagnostics are required for diagnostics and therapies, most of which are not part of SHI reimbursement (statutory health insurance) and the therapies are considered unproven or "off label use" and are also not SHI benefits.

We have developed a structured diagnostic concept based on standardised questionnaires such as the Short Form (SF-)36 Health Survey (SF- 36), Bell Score, the Canadian Criteria, the Screening for Post-Exertional Malaise (PEM), the PHQ-D (Patient Health Questionnaire) and so on. Patients are categorised according to severity, with our focus on moderate and severe cases. Patients come not only from Berlin and the surrounding area, but also from other regions and are often seen in advance via video consultation to determine the best possible therapy.

We also treat patients as part of a trial scheme (register study at the Charité based on Section 137e (2) of the Fifth Book of the German Social Code (SGB V)) and are therefore able to carry out the established but costly procedure of plasmapheresis at the expense of the statutory health insurance scheme. We also supplement our therapies supportively with medicines from anthroposophic medicine and phytotherapy.

Dtsch Z Akupunkt 2025 - 68 (1): 10-13
https://doi.org/10.1007/s42212-024-00707-4

Adopted: 25 November 2024
Published online: 6 January 2025

Pathophysiology

In terms of pathophysiology, there is no significant difference between PCS and PVS. A distinction must be made between the two if myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has occurred due to other diseases, where Epstein-Barr virus (EBV) or other infections are often blamed.

> "The pathophysiology of PCS/PVS is complex and involves various immunological mechanisms

The pathophysiology of PCS and PVS is complex and involves various immunological mechanisms (**Table 1**):

1. *Formation of GPCR autoantibodies (80-90 % of patients)*
   The largest group of patients develops G-protein-coupled receptor autoantibodies (GPCR-AAK), which arise through immunological mimicry after exposure to the spike protein of the virus or vaccines [1, 2]. These autoantibodies bind not only to the spike protein, but also to adrenergic receptors such as an- giotensin-converting enzyme 2 (ACE2), angiotensin 1 (AT1) alpha 1, beta 1, beta 2, endothelin 1 (ET1) and muscarinic 2 (M2) receptors and lead to a long-lasting stimulation (1-3 weeks; so-called agonistic long-term binding). The individual subgroups of AAK are responsible for symptoms such as tachycardia/postural tachycardia syndrome (POTS), myopathy and muscle weakness, fatigue (ME/CFS), brain fog and

Tab. 1 Pathophysiology of post-COVID-19 (PCS) and post-vaccination syndrome (PVS)

Pathophysiology	Frequency approx. (%)	Reference
Permanent stimulation of α1, AT1, β1, β2, M2, ET1 and ACE2 receptors by GPCR autoantibodies	80-90	[1, 2]
Spike protein persistence in plasma, peripheral monocytes or exosomes	8-30	[3, 4]
Microthrombotic progression triggered by spike protein persistence, endothelitis or complement activation	5-15	[6-10]

ACE2 angiotensin-converting enzyme 2; *AT* angiotensin; *ET* endothelin; *GPCR* G-protein-coupled receptor; *M2* muscarinergic-2 receptors

Dysautonomia. The agonistic continuous stimulation of the adrenergic receptors leads to "burn-out" of the permanently stimulated cells (metabolic exhaustion) and the above-mentioned symptoms and, with increased activity, to post-exertional malaise (PEM), which patients often call their crash, and to cognitive impairment.

2. *Spike protein persistence (15 % to 30 %)*
In a subgroup of patients, the spike protein persists in the body [3, 4]. The spike protein itself is highly thrombogenic and is also the antigen for the formation of GPCR-AAK, as the spike protein itself binds to the ACE2 receptor [5] and this belongs to the GPCR class. Immunologically, this can lead to a persistent pro-inflammatory reaction. This spike persistence can be detected in serum, immune cells and exosomes. The immune cells in particular are the non-classical monocytes (CX3CR1 monocytes), which are activated by physical activity and can lead to movement intolerance, cognitive problems and vascular inflammation.
3. *Microthrombotic progression (5-15 % of patients)*
Another subgroup of patients develops a more microthrombotic course of the disease, which is characterised by impaired capillary perfusion as a result of microthrombi and sludge formation in the capillaries [6-10]. The cause may be spike protein persistence or endothelitis due to ET1-AAK or complement activation.

Diagnostics

The diagnosis of PCS/PVS syndromes requires specialised laboratory specialised laboratory procedures to identify the various pathophysiological mechanisms:

1. *Determination of bioactive GPCR-AAK*
Bioassays are necessary for the detection of GPCR-AAK, as simple ELISA tests have no clinical relevance and can lead to false-positive results. Unfortunately, there are currently only 3 laboratories in Germany that commercially offer bioassays for GPCR-AAK (E.R.D.E-Labor; Berlin Cures and Cell-Trend). These bioassays, i.e. the detection of bioactive antibodies with agonistic receptor binding, help to determine the functional activity of GPCR-AAK and do not correlate with simple ELISA tests for GPCR-AAK.
2. *Spike protein persistence/spicopathy*
The persistence of the spike protein in the body is detected using specialised laboratory tests (e.g. MMD laboratory in Magdeburg). Spike proteins are analysed in plasma, in peripheral blood mononuclear cells (PBMC) and in exosomes. This differentiation is important, as different the- rapies must then be used for the various spike protein detec- tions.
3. *Diagnosis of the microthrombotic process*
Nailfold capillary microscopy is the method of choice for detecting microthrombotic changes in the capillaries [11]. Typical findings include calibre variations, ectatic capillaries, megacapillaries, tortuosities, elongations as well as sludge and thrombus formation.

Therapy and treatment options

The treatment of PCS and PVS depends on the clinical severity and the underlying pathophysiological mechanisms. Some mechanisms have not yet been conclusively researched, and the long-term efficacy also still needs to be clarified.

The following approaches are currently being trialled:

1. *Therapy of spike protein persistence in serum*
The elimination of the spike protein in the serum, whereby spike protein is then usually also found in the peripheral blood monocytes (PBMC) and possibly exosomes, is crucial in microthrombotic disease processes and in the presence of GPCR-AAK, a prerequisite for therapy, as the spike protein is the antigen for GPCR-AAK formation.
Immunoadsorption apheresis therapy to eliminate GPCR-AAK is only successful in the long term if there is no spicopathy.
Currently, the most effective therapy scheme for spike protein elimination when spike protein is detected in serum/plasma, usually also associated with low concentrations in the PBMC, is a 4-fold therapy consisting of: - Ivermectin (0.2 mg/kg body weight) over 4 weeks. With low spike protein concentrations (< 40 pg/ml), ivermectin administration in weeks 1 and 4 is usually sufficient. (Ivermectin can be administered cost-effectively as an extemporaneous preparation, which can be prescribed due to "off label use" and is to be borne by the patient);
   - Nattokinase (2× 2000 FU) for 4 weeks;
   - Bromelain (2× 4 capsules per day) for 4 weeks;
   - Acetylcysteine (600 mg) for 4 weeks.
2. *Therapy of spike protein persistence in PBMC*
If the spike protein is only detected in peripheral blood monocytes (PBMC), these are almost exclusively so-called CX1-CR3-peripheral monocytes, which can be treated with maraviroc,

a CCR5 inhibitor used in HIV treatment [12]. The duration of treatment depends on the concentration of the spike protein in the PBMC and is administered for at least 2-4 weeks.

3. *Therapy of the exosomal spike protein*
   Spike protein is partially encapsulated by the cells in membranes and secreted from the cells as exosomes. This means that these spike proteins located in membranes are hardly accessible to drug therapy and can only be achieved through a combination therapy of the above-mentioned 4-fold therapy and whole-body hyperthermia with a target temperature of 39.5 °C, as the latter destabilises the exosomes and promotes the release of the spike protein.
4. *Treatment of severe PCS/PVS with GPCR-AAK detection*
   The most efficient therapy for elimination of GPCR-AAK is currently immunoadsorption apheresis (IA; [13, 14]). This involves 5 sessions within 14-16 days, both to maximise the primary elimination of GPCR-AAK and to maximise the effect of the therapy.
   Reduction of autoantibodies
   The aim is to gradually take into account both the reduction of autoantibodies and the post-diffusion of newly dissolved AAK into the plasma. Accompanying whole-body hyperthermia can increase the efficiency of IA, as the release of bound GPCR-AAK from the tissues is promoted and these can then be increasingly eliminated from the plasma by means of IA.
   Whether a simultaneous therapy against B cells using ocrelizumab (anti-CD20-AK; [15, 16]) or inebilizumab (anti-CD-19-AK; [17, 18]), drugs that inhibit autoantibody
   The question of whether a drug that inhibits autoantibody formation in multiple sclerosis can achieve long-term freedom from GPCR-AAK is the subject of current research.
5. *therapy of microthrombotic PCS/PVS*
   Patients with a microthrombotic course without detectable spike proteins are treated symptomatically based on anticoagulation. This involves the use of platelet aggregation inhibitors such as clopidogrel and, in severe cases, new oral anticoagulants (NOAC) or direct oral anticoagulants (DOAC).
6. *Complementary and integrative medicine*
   In addition to the above-mentioned therapies, complementary approaches from anthroposophic medicine are also used. These include phytotherapeutics that have a regulating effect on various organ functions, such as hellebore or arnica planta tota for the treatment of brain fog (see also [19])

Implications for future research

The treatment of PCS/PVS remains a challenge, especially in view of the diverse pathomechanisms and insufficiently validated laboratory diagnostics. Future research must clarify how the persistence of the spike protein can be prevented and how exosomes can be effectively degraded. Further studies are also required to assess the effectiveness of immunoadsorption therapy in the long term. The continued use of the aptamer (BC007; rovunaptabine), with binding of the GPCR-AAK, must also be evaluated after the through-

phase II study is being pursued and, if necessary, brought to market launch through a marketing authorisation study.

Recommendations for patients Young women without a risk profile who are very athletic are more likely to be affected, as these people can activate well on adrenaline and therefore have a higher level of adrenergic receptors on their body cells and muscles. However, this also means that we are dealing with a clientele that is performance-orientated and desperate to get out of the crisis and has a high level of intrinsic motivation. As a result, as soon as they feel better, many of them immediately overtax themselves again. For patients with PCS/PVS, it is crucial to carry out appropriate training that avoids overloading (pacing). It is recommended to start with a simple exercise programme at home before a rehabilitation programme in order to avoid overstraining (PEM) in the rehabilitation clinic and thus a worsening of the symptoms. This means that we need an exercise programme, e.g. starting with simple isometric exercises. Muscle contractions that can be done very well at home. Adapted exercises with pacing are of central importance here.

> "Adapted cognitive training should also be cognitive training

Appropriate cognitive training should also be carried out for brain fog - there are now prescription apps for this (DiGA - digital health applications; e.g. NeuroNation Med PZN 18787822). The avoidance of unsuitable dietary supplements should also be considered, e.g. the continuous intake of nattokinase can lead to an increase in the thrombogenic risk or the dietary supplements interact with other medications, so that the patient's own medication and dietary supplements often have to be reduced.

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Compliance with ethical guidelines

Conflict of interest. H. Matthes declares that there is no conflict of interest.

No studies on humans or animals were carried out by the authors for this article. The ethical guidelines stated there apply to the studies listed.