BCG vaccination as a treatment option for ME/CFS and Post Covid Syndrome ?

HYPOTHESIS: The Bacillus Calmette–Guerin (BCG) vaccine has notable “trained immunity” effects and was shown to have therapeutic effects in autoimmune diseases like type 1 diabetes (T1D) and Multiple Sclerosis (MS). This most commonly used vaccine worldwide may also be a treatment option for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), if related or unrelated to Post Covid Syndrome (PCS).

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There is evidence that viral reactivation and/or the immunological consequences thereof may be a central part in the pathobiology of ME/CFS and PSC, with Epstein Barr Virus (EBV) reactivation apparently playing a prominent role.(1–14) In this respect ME/CFS and PCS seem to fit in with other immune related disorders including Lupus erythematodes (SLE), Sjögren Syndrome (SS), MS and T1D, in which altered immune responses to EBV have also been documented (for a review and further references, see (15)). Converting activated intracellular microbes back into a latent stage on a durable or permanent basis is difficult with classical anti-viral medications.(15)

BCG, in use since 1921, was shown to have several non-specific effects (i.e. effects reaching beyond the prevention of tuberculosis related diseases) which all relate to its ability to stimulate or modulate immune functions. These effects include anti-cancer effects (BCG is broadly used as effective therapy for non-invasive bladder cancer)(16), clinical mitigation of infectious diseases including respiratory syncytial virus, human papilloma virus, herpes simplex virus (17) and malaria(18), but also disease modifying effects in a range of autoimmune diseases. For instance, in humans with early onset T1D repeated BCG vaccinations (3 shots within 2 years) were shown in a double-blind, randomized controlled trial to induce long-term clinical remission.(19–21) Blood glucose was restored to near normal, even in patients with advanced disease of >20 years duration. In Multiple Sclerosis (MS) – a disease now understood to be pathobiologically related to a maladapted response to an infection with EBV - a single dose of BCG vaccine was shown in another double-blind, randomized controlled trial to prevent progression to clinically definite disease when given after a first demyelinating event.(22,23) Follow-up during the trial showed that the clinical effect of BCG was even more pronounced at 5 years after vaccination. BCG vaccination was also shown to have preventive immune effects, including increasing resistance against childhood leukemia(24) and atopic dermatitis.(25) Also, BCG may prevent or delay disease onset in juvenile T1D(19,26) and was shown to be 92% effective in preventing COVID-19 in patients with T1D.(27)

BCG may be a therapeutic option for ME/CFS and PCS

From these observations - some studied on a high evidence level – it appears plausible that BCG vaccination could also have disease modifying effects in ME/CFS. This appears plausible for several reasons:

First, BCG vaccination seems to be therapeutically effective in disorders with a pathobiological matrix similar to ME/CFS - like MS, where an aberrant immune response against re-activated EBV (involving clonally expanded B-cells) seems to play a central role.(28,29)

Second, BCG vaccination has documented anti-viral effects on human herpesviruses (for a summary, see (17), an observation which has already led others to suggest that „BCG administration might be considered as treatment to prevent reactivation of latent viruses, such as varicella zoster virus (VZV), cytomegalovirus (CMV) or Epstein–Barr virus (EBV)".(17)

Third, the immune effects of BCG vaccination seem to contribute to a dampening and balancing of systemic inflammation.(30) is thought to be based on the expansion of regulatory CD4+ T-cells (Treg). BCG vaccination was indeed shown to be associated with gradual demethylation of most of the signature genes expressed in highly potent Tregs, like Foxp3, TNFRSF18, CD25 and IL2.(31,32) The fact that these changes occur on the epigenetic/transcriptional level and apparently also involve bone marrow stem cells(33) may explain the long latency between BCG vaccination and clinical effects of around 2 years in the T1D and MS trials.(32)

Fourth, the immune effects documented for BCG in laboratory, animal and human studies seem to include immune-metabolic changes that include aerobic glycolysis pathways in lymphocytes. At least in the T1D trials, BCG seems to shift glucose metabolism from overactive oxidative phosphorylation with its low utilization of glucose towards accelerated aerobic glycolysis – possibly explaining the BCG effect on blood glucose levels in these T1D trials.(21,34) It is possible that this may be of benefit in ME/CFS where CD4+ and CD8+ T cells were found to have reduced glycolysis at rest (while CD8+ T cells also had reduced glycolysis following activation).(35)

Fifth, the immune effects of BCG also include induction of tumor necrosis factor alpha (TNFα) with subsequent reduction of cytotoxic (including autoreactive) T-cells(20,36,37) which may explain the effects of BCG in MS with its pathogenetic background of autoreactivity. A similar background of autoreactivity has been found in ME/CFS and PCS.(38–41)

A somewhat similar vaccine intervention that appears to be related to non-specific immune effects has already been shown to be possibly effective in ME/CFS – see the randomized controlled trial with a staphylococcal vaccine (Staphypan) by Gottfries.(42) However, patient selection may not have been rigorous in this study and may also have included fibromyalgia patients. Unfortunately, the vaccine used is not on the market any more, also, the intervention included monthly administration of the vaccine.

On a broader and more principal level, the effect of BCG might be in accordance with the "hygiene hypothesis"(20) and similar theories (e.g. 'old friends hypothesis').(43) According to these explanations, the modern epidemic of pathogen-triggered or pathogen-related immune dysfunctions - like T1D, MS, ME/CFS, SLE, SS, etc. - may be a reflection of an evolutionary mismatch situation in which the evolutionarily evolved stalemate between the endogenous microbiome and the defensive competence of the immune system is breeched. Evolutionarily, the defensive competence of the immune system has been guaranteed (among other influences like beta-glucans), by constant „built-in" immune stimulation through highly diverse species of commensal microbes, which, since the

times of the Neanderthals, also included mycobacteria. It has long been known, for instance, that tuberculosis itself protects from both T1D and MS.(44,45)

From these considerations it may appear plausible to mimic these “old friends” with interventions now widely discussed as “trained immunity” interventions.(46,47) Here, there is agreement in the literature that BCG vaccination may be the most powerful inducer of “trained immunity”.(17,48,49)

Testing the hypothesis would require appropriate clinical studies. The therapeutic agent itself is cheap, safe, easily available and easy to administer. Fortunately, similar studies have already been performed on a very solid methodological level by the Faustman Laboratory at Massachusetts General Hospital (https://www.faustmanlab.org/). Their studies could therefore serve as state-of-the-art templates and cooperation would seem an obvious consideration. Especially regarding biomarkers to be followed, patient selection, dosing schedule as well as selection of the most promising BCG strain consultation with the Faustman Laboratory would be warranted.

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