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 Post Covid Syndrome (PCS) and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

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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.(1–16) 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 see (17)). Converting activated intracellular microbes back into a latent stage on a durable basis is difficult with classical anti-viral medications.(17)

BCG, in use since 1921, was shown to have several non-specific effects which all relate to its ability to modulate immune functions. These effects include anti-cancer effects(18), clinical mitigation of infectious diseases including respiratory syncytial virus, human papilloma virus, herpes simplex virus (19) and malaria(20), 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.(21–23) In Multiple Sclerosis (MS) 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.(24,25) BCG vaccination was also shown to have preventive immune effects, including increasing resistance against childhood leukemia,(26) atopic dermatitis,(27) juvenile T1D(21,28) and, in patients with T1D, COVID-19.(29)

From these observations it appears plausible that BCG vaccination could also have disease modifying effects in ME/CFS:

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 reactivated EBV seems to play a central role.(30,31)

Second, BCG vaccination has documented anti-viral effects on human herpesviruses (for a summary, see (19), an effect which may extend to symbiotic viruses: „BCG administration might be considered as treatment to prevent reactivation of latent viruses, such as varicella zoster virus (VZV), cytomegalovirus (CMV) or EBV".(19)

Third, the immune effects of BCG seem to contribute to a dampening and balancing of systemic inflammation.(32) This effect is thought to be based on the expansion of regulatory CD4+ T-cells (Treg). BCG vaccination was associated with gradual demethylation of signature genes expressed in highly potent Tregs, like Foxp3, TNFRSF18, CD25 and IL2.(33,34) The fact that these changes occur on the epigenetic/transcriptional level and apparently involve bone marrow stem cells(35) may explain the long latency between BCG vaccination and clinical effects of around 2 years in the T1D and MS trials.(34)

Fourth, the biological effects of BCG administration seem to include immune-metabolic changes with a shift of glucose metabolism from overactive oxidative phosphorylation towards accelerated aerobic glycolysis – possibly explaining the BCG effect on blood glucose levels in the T1D trials.(23,36) 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).(37)

Fifth, the immune effects of BCG also include induction of tumor necrosis factor alpha (TNFα) with subsequent reduction of cytotoxic (including autoreactive) T-cells(22,38,39) 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.(40–43)

On a broader and more principal level, the effect of BCG might be in accordance with the "old friends hypothesis".(44,45) 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 calibrated 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.(46,47)

From these considerations it may appear plausible to mimic these "old friends" with interventions now widely discussed as "trained immunity" interventions(48,49), of which BCG vaccination may be the most powerful option.(19,50,51)

BCG is cheap, safe, easily available and easy to administer. Rigorous BCG studies have been performed 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.

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