Research protocol

VIRAL-MI: Profiling vulnerability and resilience for mental illness following viral infections: translating epidemiology to deep-phenotyping

Abstract

Infectious diseases are known to significantly increase the risk for later development of a mental disorder. A growing body of research has further demonstrated that individuals with a pre-existing mental disorder are vulnerable to more severe post-infection outcomes. Different mechanisms have been suggested to mediate these associations, while suggesting that neurobiological changes triggered by the infection can serve as a common pathophysiological factor. At the same time, environmental risk factors have also been suggested to contribute to both the increased risk of mental disorder and severe post-infection outcomes. Nonetheless, to date no study has integrated neurobiological, genetic, inflammatory, social, and psychological factors as risk or resilient determinants to provide a comprehensive model of the phenomena. In this state-of-the-art joint transnational study, we aim to investigate the interplay between viral and other clinically relevant infections and mental disorders, starting from epidemiology and proceeding with deep phenotyping of involved variables. Based on extensive empirical and theoretical formulations, we hypothesise that post-infection inflammatory status and its effects in the brain will serve as a shared mechanism for subsequent development of mental illness, as well as for the worse infection outcomes observed in individuals with pre-existing mental disorders. Environmental risk and resilience factors are hypothesised to further moderate these associations. Exploiting wide epidemiological databases (Israel and Norway), deep-phenotyped cohorts (Italy and Belgium), and state of the art neuroimaging techniques and transcriptomics, we will map the immune and neurobiological underpinnings for individual vulnerability or resilience, as well as their interaction with environmental factors in response to viral and other clinically relevant infections. Multimodal neuroimaging, genetic, and immunophenotyping assessments combined with social, economic and cultural factors will be integrated with machine learning analyses to stratify patients according to potential untracked subpopulations and generate individual predictive signatures of vulnerability versus resilience to negative mental and physical outcomes. Finally, state of the art transcriptomic analysis will be performed in proof-of-concept studies to identify druggable targets. This joint collaborative effort can set the stage to consider new personalised therapeutic and preventive strategies, as well as to broaden the scientific exploration of druggable targets to eliminate the adverse consequences of infections.

Protocol summary of workplan 2 (Israel, PI Dana Tzur Bitan)

The following sections are derived from the full protocol submitted to ERA-NET NEURON on June 30, 2023, and describe the protocol for the Israeli site. Reference numbers have been adjusted to align to the relevant text.

Background

Severe infections, requiring hospitalization settings, have been shown to significantly increase the risk for later schizophrenia or mood disorders by 60 - 63% (1,2). More recently we demonstrated that clinically significant depressive psychopathology was present in approximately 30–40% of patients up to 12-month follow-up after SARS-CoV-2 infection, % defined from new psychopathological onset (3), and that severe MI showed an increased COVID-19 morbidity and mortality compared to controls, regardless of sociodemographic and medical factors (4).

Hypothesis

History of viral infections will be associated with increased risk for later development of a MI, as well as with psychiatric relapse among individuals with pre-existing MI.

Methods

The Israel cohort consists of two databases from the Clalit Health Services (CHS) registries from Israel (CHS1 n=50,000, CHS2 n=69,594). The CHS is the largest of four operating healthcare organisations to provide healthcare to all citizens of Israel, and covers more than 50% of Israel's population. The CHS databases undergo periodic updating processes and have been validated by the registry algorithm as well as by many scientific organisations utilising the database. The diagnoses of chronic diseases are based on real-time input from healthcare providers, pharmacies, medical care facilities, and administrative computerised operating systems. Psychiatric Diagnoses are based on the ICD-9 and ICD-10 classifications. To evaluate probability of MI following infection and post-infection outcomes (CHS1), individuals with a high load of past infections will be identified and matched in a 1:1 ratio to controls by age and sex. Probability of MI onset across a broad range of psychiatric disorders will be explored among the high load and control groups, including depression, BD, anxiety and psychotic disorders. Inclusion criteria: individuals insured by the CHS since birth and with at least 10 years of follow up; exclusion criteria include termination of insurance and lack of successive medical follow up. To evaluate the probability of psychiatric relapse among individuals with pre-existing mental disorder following infection (CHS2), a cohort of 34,797 individuals with schizophrenia matched randomly to age and sex HC with no diagnosis of schizophrenia will be exploited. Inclusion criteria for this sample is an active diagnosis of schizophrenia in CHS registries during stages of analyses, and place of residence is at the CHS hospital catchment areas (to ensure psychiatric hospitalisation is fully registered); exclusion criteria include lack of active diagnosis and place of residency outside of CHS catchment area. Across both cohorts, socioeconomic status, familial status, marital status, number of siblings, smoking, obesity, diabetes, hypertension, hyperlipidemia, chronic

obstructive pulmonary disease and ischemic heart disease, as well as healthcare utilisation and other demographic variables have been collected. The following infections will be considered across both cohorts: Epstein Barr Virus, Cytomegalovirus, Toxoplasma Gondii, COVID-19, and Herpes viruses. Measures of inflammation include neutrophil/lymphocyte ratio and systemic inflammatory index.

Power and sample size considerations

To maximise accuracy, restrictive estimates of the least prevalent MIs were utilised for sample size estimation. Based on O'Donoghue et al. findings (5), first episode psychosis before COVID-19 epidemic was 104.5 per 100,000 with an incidence rate ratio after the pandemic of 1.94. Assuming that at least some of the variance in psychosis incidence is associated with post-viral infection, we estimate sample size needed to detect exposure (infection) impact with. 80% power and 95% Ci, the $\chi 2$ test with continuity correction indicated that the most conservative estimated sample size needed to detect such difference was 27,168. Thus, the sample size of both the Israel and Norway cohort far exceeds the minimum sample size needed to produce the most conservative estimates.

Statistical Analysis

To demonstrate an association between infections, with a particular focus on viral ones, severe MI and post-infection severe outcomes (Objective 1), we will compute hazard ratios (HRs) to assess the risk of SMI development or psychiatric relapse following infection using Cox proportional hazard regression models in all three cohorts (CHS1, CHS2, MoBa). Incidence rates and crude and adjusted models controlling for demographic and clinical factors will be reported. The proportional hazard assumption will be tested as the correlation between the Schoenfeld residuals and survival time, with significance level of $p<0.05$ indicating non-proportionality. Estimated projections of the cumulative probability of severe outcome among individuals with pre-existing SMI will be obtained by Kaplan-Meier analysis. Confounding, moderation and mediation patterns of environmental (socio and sociodemographic) and biological (inflammatory, polygenic risk score (PRS) for MI and immune-related conditions) mechanisms will be assessed using the PROCESS macro, a simulation-based strategy based on re-sampling (bootstrapping) techniques. Direct and indirect effects, standard errors and confidence intervals will be estimated based on the bootstrap distribution found with 10,000 bias-corrected resamples. PRS will be computed following the method described by Purcell et al. (6) Analyses will be performed based on the directed acyclic graph (DAG) causal framework, ensuring transparent model assumptions and minimising bias. All three databases provide nation-wide representative data and have proven their efficiency in characterising MI cohorts and associations with environmental factors, as shown by high impact publication (7,8).

Relevant references

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