Brazil-China Innovation Dialogue

Frontiers in Medicine and Public Policy Challenges II

How to implement precision healthcare in the SUS

PRECISION MEDICINE: IDENTIFICATION OF BIOMARKERS IN AUTOIMMUNE DISEASES OF THE CNS AND BY VIRAL TRIGGERS

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Brazil has reached a life expectancy close to that of developed countries and is undergoing a clear demographic transition. The literature has shown that some diseases associated with certain biomarkers (BM) almost tripled during the COVID-pandemic, and some of these BMs, applied in the diagnostic criteria for Autoimmune diseases (AID), have been identified in the acute or post-infectious phase by SARS-CoV-2 and in post-infectious autoimmune phenotypes by arboviruses. The increase in AID and neurodegenerative cases in Brazil represents a challenge for the health system, as it will mean a considerable increase in public spending to create and maintain the infrastructure necessary for patients. Therefore, a major focus of the Brazilian health system should be increasingly on these diseases, many of which are influenced by environmental factors. The majority of AID and neurodegenerative diseases remain without adequate diagnostic methods, complicating the therapeutic management of patients.

Additionally, some infectious and autoimmune diseases that overlap inflammatory and degenerative mechanisms have been associated with diagnostic and monitoring BMs. However, BM information is still rarely used to determine individual management, which could lead to more effective therapeutic strategies. This set of resources and individualized management for early diagnosis and treatments is called "Precision Medicine," which in the Brazilian population is restricted to a few patients with access to plasma BM research and genetic investigation. This gap has been minimized in reference centers, like ours at UNIRIO and UFRJ for 20 years.

Autoimmune diseases of the central nervous system (CNS) represent heterogeneous phenotypes, associated with diagnostic biomarkers (BM) with variable sensitivity and specificity. Clinico-radiological and molecular mimicry are identified in association with viral triggers. Among the CNS AIDs, the most notable are Multiple Sclerosis (MS), Neuromyelitis Optica spectrum disorder (NMOSD), diseases associated with anti-myelin oligodendrocyte glycoprotein antibody (MOGAD), acute disseminated encephalomyelitis (ADEM), and Autoimmune Encephalitis (AE) associated with autoantibodies that direct neuroglial antigens to different receptors such as N-methyl D-Aspartate (NMDAR), gamma-

aminobutyric acid A receptor (GABAAR), contactin-2 (CASPR2), glial fibrillary acidic protein (GFAP), oligodendroglial glycoprotein of myelin (MOG), aquaporin-4 (AQP4), and others.
It is time to apply the methodology of the SIMOA Platform (ultrasensitive single-analysis molecule) and the ILUMINA Platform for genome-wide analysis (GWAS) to: i) Expand the identification of plasma BM and GWAS associated with neurological, radiological phenotypes, and outcomes in CNS AID; ii) Identify the radiological and morphological neurological patterns of CNS infection and post-infection by CHIKV, ZIKV, and DENV, and correlate with BM and GWAS; iii) Categorize the correlation between CNS manifestations in the acute and post-infectious phase of SARS-COV-2 with BM (anti-NMDAR, anti-CASPR2, anti-GAD, TAU, GFAP, NfL, and UCHL1); iv) Identify genetic risk factors by genome-wide screening (GWAS) in AID cohorts, including post-viral triggers, in parallel to preclinical studies; v) Correlate findings to

advance the search for neuroinflammatory and autoimmune patterns by deploying advanced computational biology statistical approaches (including supervised machine learning) to identify clinical and molecular patterns that may be potential disease markers or therapeutic targets.
Implementing routine diagnostic biomarkers such as anti-AQP4, anti-MOG, anti-NMDAR, anti-CASPR2, anti-GAD, and anti-GD1a, as well as activity and neurodegeneration biomarkers NfL, GFAP, UCHL-1, and TAU protein, is a leap forward for scientific and technological development in Rio de Janeiro. The relevance of identifying genetic risk factors underlying many rare and common neurological diseases such as CNS autoimmune diseases is indisputable and contributes to redefining spectrums of overlapping phenotypes, proposing hypotheses to be tested in animal models, as we did with the identification of TLR4 in patients with COVID-19, before seeking proof of concept in animal models, and identifying new therapeutic targets.
It is worth mentioning that most gene banks do not include Brazilian patients, a population with different characteristics from the GWAS studies available, with sequence databases mostly from Caucasians. Although human GWAS have discovered numerous susceptibility genes for the CNS autoimmune diseases cited here, the odds ratios associated with risk alleles are generally low and represent only a small proportion of estimated inheritance. Next-generation sequencing (NGS) technologies such as whole-genome sequencing and wide exome sequencing (WES) have enabled the rapid identification of rare variants, contributing to the understanding of the basis of many Mendelian methods of neurological conditions, as well as complex neurological diseases such as those studied here