PROJECT

Supervisor:	Dr. Federica Esposito
Title:	Biological Deconvolution of Central Nervous System Inflammatory Disorders Not Otherwise Specified Through Integrated Clinical, Biomarker and Immunogenetic Profiling
Curriculum:	Neurosciences and Experimental Neurology
Link to the personal page of the University or relevant hospital site website:	https://research.hsr.it/en/institutes/institute-of-experimental-neurology/human-genetics-of-neurological-disorders/federica-esposito.html

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge: Inflammatory demyelinating diseases of the central nervous system (CNS) that do not fulfil current diagnostic criteria for multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD) or myelin oligodendrocyte glycoprotein–associated disease (MOGAD) represent a clinically challenging category. These "CNS inflammatory diseases not otherwise specified (NOS)" cases are highly heterogeneous in clinical presentation, MRI features and cerebrospinal fluid (CSF) findings. Some of them likely represent early or abortive forms of defined entities, particularly MS, whereas others may constitute distinct immune-mediated conditions or overlap with vascular leukoencephalopathies. Currently, no structured framework exists to stratify these patients, and the absence of dedicated diagnostic criteria results in diagnostic delays, uncertainty in therapeutic decision-making and lack of evidence-based guidance for follow-up strategies.

Rationale and hypothesis: We hypothesize that CNS inflammatory NOS cases are not biologically homogeneous but can be deconvoluted into: (i) patients aligning along a continuum with established inflammatory disorders (e.g., early phase of MS), and (ii) a residual subgroup with distinct clinico-radiological and immunogenetic features. An integrated approach combining deep clinical phenotyping, targeted biomarker profiling and HLA genetic analysis may help in identifying biologically coherent subgroups and improve diagnostic positioning.

Objectives and specific aims

Aim 1. To perform structured clinical characterisation of CNS inflammatory disease NOS, including clinical course, MRI features, and CSF parameters (oligoclonal bands, blood-CSF-barrier impairment) obtained from standard clinical routine.
Aim 2. To position NOS cases along a biological continuum relative to MS, NMOSD, MOGAD and other established inflammatory diseases of the CNS, using supervised modelling approaches followed by unsupervised clustering of poorly assigned cases.
Aim 3. To identify and characterise residual CNS inflammatory disease NOS subgroups through integration of targeted candidate biomarker analysis (focused panel of selected proteins) and HLA-based genetic stratification.
Expected outcomes: The results from this project are expected to provide a biologically informed stratification framework for CNS inflammatory diseases NOS; in particular, it will help distinguishing early/abortive forms of known autoimmune CNS diseases from potentially distinct entities. Additionally, this study will validate candidate biomarkers supporting differential diagnosis among these entities. Finally, it will generate preliminary data for hypothesis-driven mechanistic studies, as well as future multicentric validation studies.

Skills that the student should acquire (max. 600 characters including spaces):

Clinical data harmonisation and structured phenotyping, using also standard MRI and CSF data available from clinical practice; design and interpretation of targeted candidate biomarker assays; HLA-based genetic data extraction and risk allele analysis; multidimensional data integration; supervised and unsupervised statistical modelling; biostatistics and translational research methodology.

References (max. 15)

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