Systemic cytokines and GlycA discriminate disease status and predict corticosteroid response in HTLV-1-associated neuroinflammation

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Background:

No disease-modifying therapy exists for HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP), but corticosteroids provide some clinical benefit. We investigated systemic cytokines and a novel chronic inflammatory marker, GlycA, as possible biomarkers of immunopathogenesis and therapeutic response in HAM/TSP, and examined their interaction with established risk factors (age, sex, proviral load).

Methods:

We recruited 110 People living with HTLV-1 (PLHTLV-1, 67 asymptomatics and 43 HAM/TSP patients, total 946 person-years of follow-up). Plasma cytokine levels (IL-2/IL-4/IL-6/IL-10/IL-17A/IFN-γ/TNF) and GlycA were quantified by Cytometric Bead Array

and ^{1}NMR, respectively. Cytokine signaling and prednisolone response were validated in an independent cohort by nCounter digital transcriptomics. We used multivariable regression, machine learning and Bayesian networks for biomarker identification.

Results:

We found that systemic IL-6 was positively correlated with both age ($r=0.50$, $p<0.001$) and GlycA ($r=0.45$, $p=0.00049$) in asymptomatics, revealing an 'inflammaging" signature absent in HAM/TSP. GlycA levels were higher in women ($p=0.0069$), but cytokine levels did not differ between the sexes. IFN-γ ($p=0.007$) and IL-17A ($p=0.0001$) levels were increased in untreated HAM/TSP. Multivariable logistic regression identified IL-17A and proviral load as independent determinants of clinical status, with modest accuracy of predicting HAM/TSP status (64.1%), while a machine learning-derived decision tree classified HAM/TSP with 90.7% accuracy. Pre-treatment GlycA and TNF levels significantly predicted clinical worsening (Osame Motor Disability Scale), independent of proviral load. Poor prednisolone response was significantly correlated with higher post-treatment IFN-γ levels. Likewise, a transcriptomic IFN signaling score, significantly correlated to previously proposed HAM/TSP biomarkers (*CASP5/CXCL10/FCGR1A/STAT1*), was efficiently blunted by in vitro prednisolone treatment of PBMC from PLHTLV-1 and incident HAM/TSP.

Conclusions:

An age-related increase in systemic IL-6/GlycA reveals inflammaging in PLHTLV-1, while absent in HAM/TSP. IFN-γ and IL-17A are biomarkers of untreated HAM/TSP, while pre-treatment GlycA and TNF predict therapeutic response to prednisolone pulse therapy, paving the way for a precision medicine approach in HAM/TSP.

Disclosure of Interest Statement:

All the authors declare no conflict of interest.