VAC_01 - Type I interferon innate errors causing severe adverse events following yellow fever vaccination: a family-based case study

Tamiris Azamor da Costa Barros[1]; Andrea Marques Vieira da Silva[1]; Felipe Soares Coelho[1]; Lorenna Carvalho da Rosa[1]; Juliana Gil Melgaço[1]; Daniela Prado Cunha[2]; Patrícia Mouta Nunes de Oliveira[1]; Maria de Lourdes de Sousa Maia[1]; Zilton Vasconcelos[2]; Ana Paula Dinis Ano Bom[1].
[1]Fiocruz/Bio-Manguinhos
[2]All Lab/Fiocruz

Introduction: Despite being considered the gold standard vaccine, Yellow Fever Virus 17DD (YFV17DD) is associated with rare cases of neurological or viscerotropic adverse events following immunization (YEL-AVD). Although the mechanisms behind YEL-AVD cases remain elusive, its occurrence days after vaccination suggests innate immune errors (IIE).

Objectives: Here, we report a family case from a national-base, phase IV study, aiming to clarify the mechanisms behind YEL-AVD pathogenesis and identify biomarkers useful in reducing the incidence of these rare events.

Methodology: Blood samples were collected from the case and relatives 1-2 years after YF17DD immunization (CAAE 60575716.2.0000.5262). DNA was extracted followed by Whole Exome Sequence (WES) analysis, and validation of genetic findings using RT-qPCR. For functional investigation, the Peripheral Blood Mononuclear Cells (PBMC) from YEL-AD cases and nine time-matched controls were used to perform *in vitro* stimulation with attenuated YFV17DD virus, followed by immunophenotyping, luminex assay, and transcriptomics.

Results: The family is composed of 11 siblings including three YEL-AVD cases, two deceased, and one surviving brother (proband). Samples from 4 proband's nephews were also analyzed. Copy number variation analysis from WES demonstrated that the proband present homozygosity for an *IFNAR1* allele lacking exons 3, 4, and 5. The same genotype was detected in the daughter of the deceased sister. Three siblings and one nephew are heterozygous without a history of YEL-AVD. Comparing to the YFV17DD-specific response in the healthy group, the proband presented higher secretion of interferons IFN-a, IFN-b, IFN-g, IFNGR1, and the proinflammatory cytokines CXCL10, IL1-b, and CCL3. The proband presented higher frequency of activated non-classical monocytes and NK cells, and naive T cells IFN-g +. Also, the proband presented 240 exclusive upregulated genes, which were related to antiviral response through *USP18*, a negative regulator of IFN-a, and type II IFN. In addition, the proband demonstrated upregulation of inflammatory events - pyroptosis and IL-1b production.

Conclusion: The family investigated is composed of carriers of defective alleles in *IFNAR1*, the receptor that triggers the main human antiviral response: type I IFN pathway. The homozygosity of the *IFNAR1* depleted for exons 3, 4, and 5 led to YEL-AD in three family members. Our functional findings suggest the absence of type I IFN response, exacerbated type II IFN, and hyperinflammation as a repercussion of a defective *IFNAR1*, which contributes to YEL-AD pathogenesis.

Keywords: Adverse events following immunization; Yellow fever vaccine; System vaccinology