EVIDENCE OF B-CELL DYSFUNCTION IN INDIVIDUALS WITH LONG COVID-ASSOCIATED DYSAUTONOMIA

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mcoiras@isciii.es ; m.torres@externos.isciii.es

M. Torres [1,2], C. Sánchez-Menéndez [1,3], A. Simón-Rueda [1,2,4], A. García Casas [5], J. Bartolomé [1,6], L. Lemus-Aguilar [1,7], E. Mateos [1,2], J. Aguareles-Gorines [5], Guillermo Santamaría [5], M.A. Murciano-Antón [8], P. Guisado-Vasco [9], M. Coiras [1,2]

[1]Immunopathology and Viral Reservoir Unit, National Center of Microbiology, Instituto de Salud Carlos III, Madrid, Spain. [2]Biomedical Research Center Network in Infectious Diseases (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain. [3]Hematology and Hemotherapy Service, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain. [4]Infectious Diseases Unit, Internal Medicine Service, Hospital Clínico San Carlos, Madrid, Spain. [5]Hospital Universitario Quironsalud Madrid, Servicio de Investigación y Docencia, Madrid, Spain. [6]Faculty of Science, Universidad Complutense de Madrid, Madrid, Spain. [7]PhD Program in Biomedical Sciences and Public Health, Universidad Nacional de Educación a Distancia (UNED), Madrid, Spain. [8]Family Medicine Service, Primary Healthcare Center Doctor Pedro Laín Entralgo, Madrid, Spain. [9] Hospital Universitario Quironsalud Madrid, Servicio de Medicina Interna, Madrid, Spain.

BACKGROUND

- Long COVID (LC) can trigger dysautonomia or dysfunction of the autonomic nervous system (ANS) similar to some autoimmune diseases.
- Dysautonomia has been related with autoantibodies produced by activated non-specific B-cell clones that may interfere with the ANS normal function.
- **Our objective** was to analyze alterations in the humoral immunity with a specific focus on the BLyS/APRIL signaling pathway, which is essential for B-cell activation and regulation, to elucidate potential molecular mechanisms underlying dysautonomia in LC.

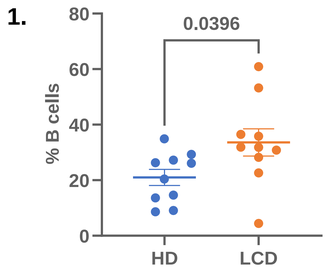
METHODS

- Comparative, observational, cross-sectional study comprising people with LC exhibiting dysautonomia (LCD; n=26) and healthy donors (HD; n=42).
- Peripheral blood mononuclear cells (PBMCs) were immunophenotyped by flow cytometry. Plasma cytokines were measured by multiplex immunoassay. Total IgG and autoantibodies were quantified by ELISA.

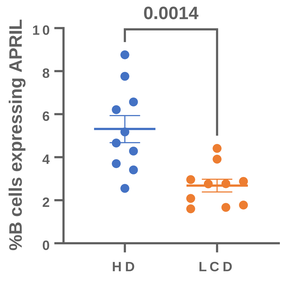
RESULTS

1) LCD participants had a median age of 46 years-old (IQR 42-52) while HD had 45 years-old (IQR 39-52); most participants were female (89 and 86%, respectively).
2) Total B cell levels (CD3-CD19+) were increased 1.6-fold in LCD compared to HD (p=0.0396) (**Figure 1**). However, the levels of total B cells and activated memory B cells (CD10-CD27+CD21low) expressing APRIL (A-PRoliferation-Inducing Ligand) on the cell surface were significantly lower in LCD (p=0.0014 and p=0.0021, respectively) (**Figures 2, 3**).

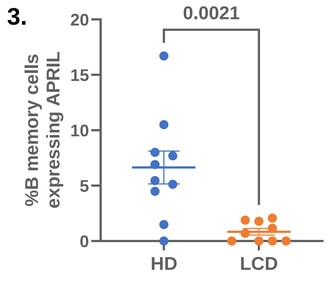
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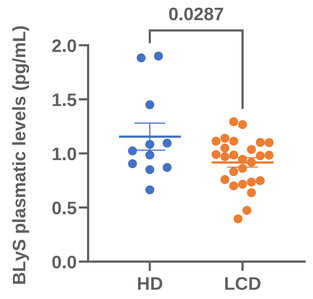
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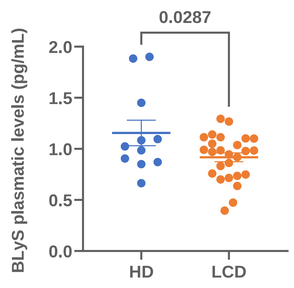
Potential B-cell dysfunction in Long COVID-related dysautonomia was associated to reduced IgG levels and BLyS and APRIL expression

3) LCD showed reduced plasma levels of both APRIL (-1.2-fold; p=0.0342) and BLyS (B-Lymphocyte Stimulator) (-1.3-fold; p=0.0287) (**Figures 4, 5**).

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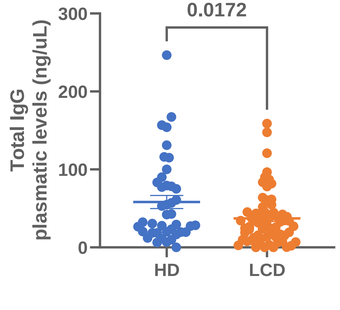


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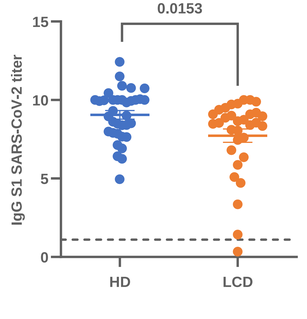


4) According to this reduced B-cell activation, total IgG levels and specific against SARS-CoV-2 were 1.6-fold (p=0.0172; and p=0.0153, respectively) (**Figures 6, 7**)

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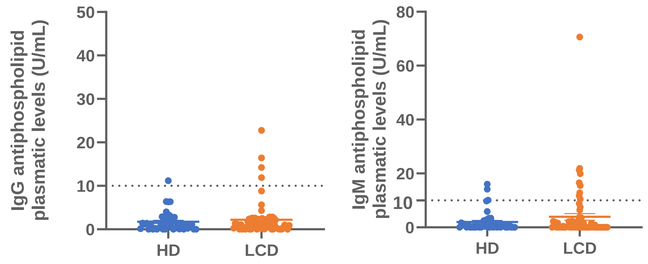
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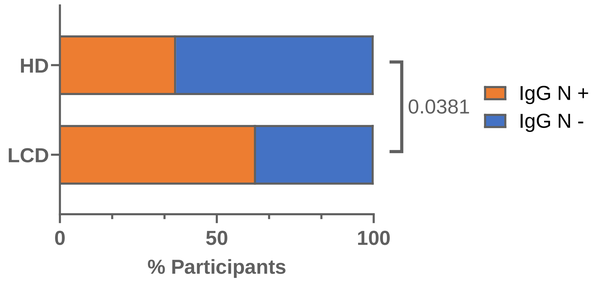
CONCLUSIONS

- Our findings showed a distinct humoral immunological profile in LCD.
- Increased levels of antiphospholipid autoantibodies may interact with the central and peripheral nervous systems, leading to neuropathies and possibly dysautonomia.
- Additionally, our LCD cohort had reduced plasma levels of total IgG despite higher total B-cell levels, coupled with decreased BLyS and APRIL expression, indicating a potential B-cell dysfunction and lower protection against SARS-CoV-2 reinfections.
- These results provide novel insights into the immunopathological mechanisms of LC-related dysautonomia and potential therapeutic targets.

5) The analysis of several autoantibodies in plasma revealed positive results only for antiphospholipid IgG and IgM in some participants with LCD



6) LCD had 2.4 times more breakthrough infections than HD (p=0.0291).



ACKNOWLEDGEMENTS

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